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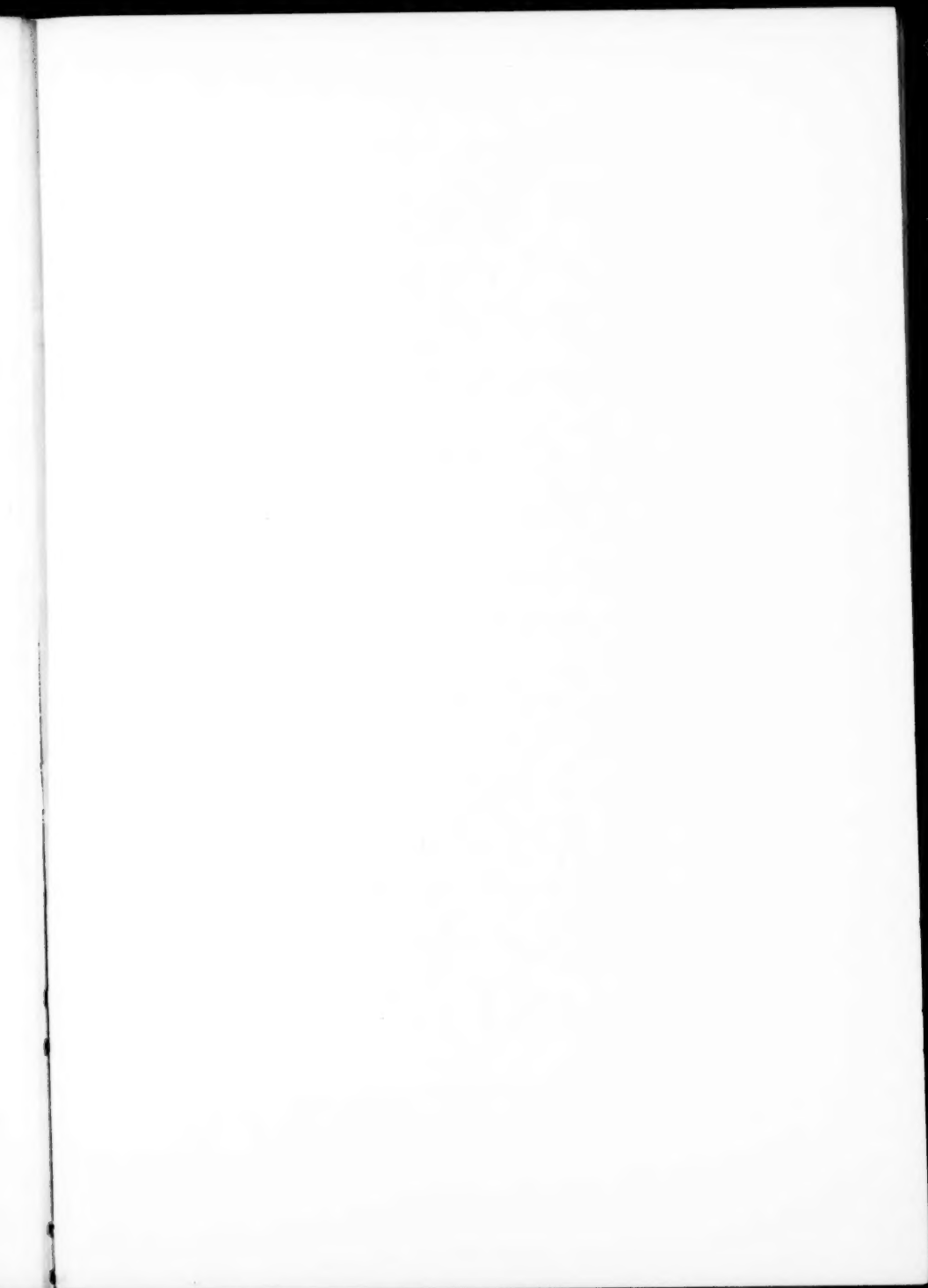
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PREFACE

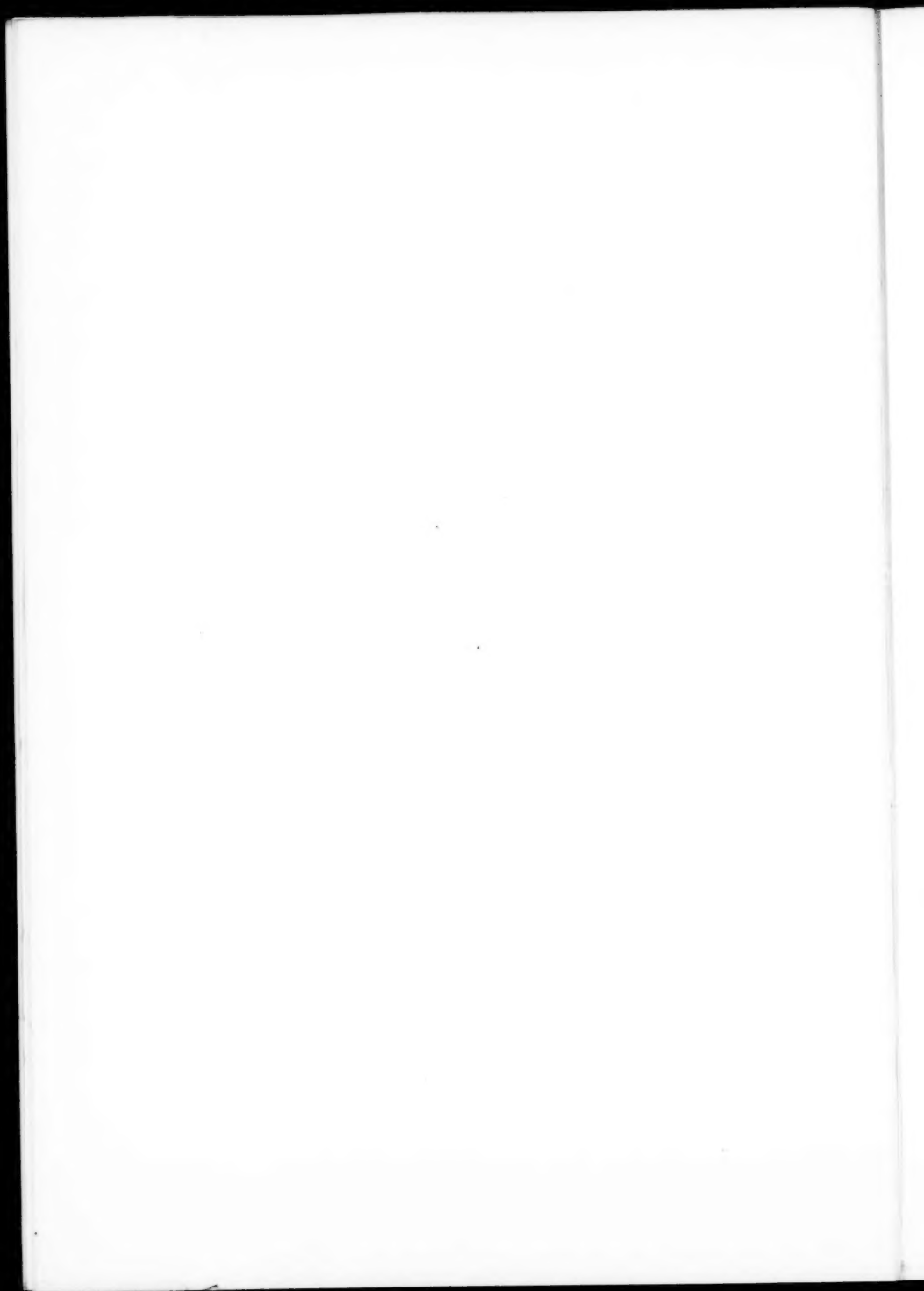
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This volume of the *Annual Review of Physiology* lacks the bulk of its predecessor for two reasons. First, three of the chapters announced for inclusion have not become available: that by Otto H. Schmitt on Bioelectric Phenomena, that by Norman E. Freeman and Rutherford S. Gilfillan on Visceral Functions of the Nervous System, and that by J. Govaerts on Water Balance. We shall try to make amends to our readers by requesting reviewers of these topics for the next volume to include in their reviews the material which would have been surveyed in the missing chapters. Second, in accordance with a policy adopted for all of the *Annual Reviews*, the type size has been reduced from ten to nine point and the size of the printed area on each page increased. This change will not affect the amount of material in the chapters, but will achieve a considerable economy.

We continue herein the policy of publishing a prefatory chapter by a leading physiologist. This year's author is Dr. Carl Wiggers whose account of his personal experiences in the first two decades of this century, against a background of the development of physiology, will be of great interest to our readers. We are including also a portrait of Dr. Wiggers, and to make complete the matching of portraits with prefatory chapters, we also include as a frontispiece one of Dr. Eugene F. DuBois who wrote the first of such chapters for our previous volume. It is our hope that those of our readers who have been privileged to know these men personally will treasure these personal reminders and that those who have not been so privileged will be able to capture some of the human qualities they so richly possessed but which are not fully evident in their more formal writings.

We hasten to disclaim any attempt to regard those who write these prefatory chapters as those worthy above all others to be considered as leaders of our profession. Others, equally notable, have been unable for various reasons to accept our invitations to write such chapters. Particularly this year, we regret that we did not obtain one from the pen of Dr. H. C. Bazett whose death during his term of office as President of the American Physiological Society came as a tragic shock to his many friends who held him in high esteem and affection.

J.F.F.	M.B.V.
M.H.J.	J.M.C.
F.C.M.	A.C.G.
R.F.P.	V.E.H.



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VOLUME XIV (1952)

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PHYSIOLOGY OF CONNECTIVE TISSUE, *C. Ragan*
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ERRATA

Volume XII

page 80, line 7: *for* glutamine, *read* glutamic acid.

page 419, line 14: *for* Hodgkin, A. F., *read* Huxley, A. F.

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CARL J. WIGGERS, M.D., Sc.D.

PREFATORY CHAPTER PHYSIOLOGY FROM 1900 TO 1920: INCIDENTS, ACCIDENTS, AND ADVANCES¹

BY CARL J. WIGGERS

*Department of Physiology, School of Medicine, Western Reserve
University, Cleveland 6, Ohio*

This article consists of an attempt to comply in part with the request of the Editor—to interpret on the basis of personal experiences the influences that have aided the development of physiology and channeled advances in the subject during the past fifty years. It was probably assumed that I was qualified for such a task because I entered medical school at practically the beginning of the century, viz., in 1901. As indicated in the title, I have chosen to confine the survey to the first two decades of the century, owing to limitations of time and space and because relative newcomers are perhaps less familiar with conditions prevailing during that period. They may even labor under the delusion that our fund of physiological information was quite meager a half-century ago and that the greatest progress has been made during the past two or three decades. This erroneous belief might excusably be derived from the facts that during the past thirty years the number of physiologists has greatly increased, laboratories have become more commodious and better equipped, enormous funds have become available for the support of research, the number of papers published in more and better journals has skyrocketed, and new discoveries have been announced very frequently, even in lay publications and over the radio.

May I, therefore, assure the present generation that the volume of physiological information that we were required to master as students was by no means small, as can easily be verified by perusal of textbooks such as those of Stewart, 1895 (1); Schäfer, 1898–1900 (2); and *An American Textbook of Physiology*, edited by Howell in 1901 (3). Candidates for a doctor's degree in physiology might well be required to have a familiarity with the material contained in such texts. A rough estimate of our stock of physiological facts in various periods of the twentieth century can be made rather quickly by comparing the contents of textbooks issued in successive years. A deeper insight can be gained by consultation of outstanding monographs, lectures, and reviews, and, since 1939, of successive volumes of the *Annual Review of Physiology*. Among textbooks useful for such a survey, the following may be mentioned: Howell, 1905 (4); Nagel 1905–09 (5); Krehl, 1906 (6); Tigerstedt, 1907 (7); Luciani, 1911–21 (8); Starling, 1912 (9); Bayliss, 1914 (10); Hewlett, 1916 (11); Macleod, 1918 (12); Höber, 1919 (13); Burton-Opitz, 1920 (14); Roaf, 1924 (15); Wright, 1926 (16); Bethe, eighteen volumes, 1927–32 (17); Martin & Weymouth, 1928 (18); Halliburton & McDowall, 1930 (19); Winton & Bayliss, 1931 (20); Gellhorn, 1931 (21); Wiggers, 1934 (22); Best &

¹ The Past-President's Address at the fall meeting of the American Physiological Society at Columbus, Ohio, September 15, 1950, was based on material in this chapter.

Taylor, 1937 (23); Heilbrunn, 1937 (24); Bard, 1938 (25); Fulton, 1940 (26); Houssay *et al.*, 1945 (27); and Hamilton, 1947 (28). Many of the foregoing have been repeatedly revised, and the dates of only the first issues are indicated. Several equally good texts have probably been inadvertently omitted.

The physiological knowledge available to us in 1900 was a heritage of previous generations. Physiology already owed a great deal to the master mathematicians and physicists of the seventeenth and eighteenth centuries and to the early physiologists who were inspired by John Hunter and Johannes Müller to make functional deductions from the structure of tissues and organs. However, the physiology of 1920 was built largely upon the experimental work of the previous century. Magendie, Legallois, Flourens, the three Weber brothers, von Liebig, Wöhler, Poiseuille, and Bowman were among the more prominent contributors of the first half of that century. Claude Bernard, Ludwig, Helmholtz, and their brilliant pupils, du Bois Reymond, Brücke, Goltz, Brown-Séquard, Kühne, Hoppe-Seyler, Kossel, and many others who worked during the latter half of the nineteenth century, made this a period of most rapid progress through use of experimental methods. Through their genius and zeal the virgin soils yielded bountiful harvests. Indeed, so great had been the crop of discoveries that those of us who entered fields of investigation early in the twentieth century felt that the law of diminishing returns must operate until the soil could be refertilized or until better tools should become available.

The physiological subjects that were most completely understood were those of nerve and muscle, special senses, and circulation. It was therefore natural that these should be more extensively emphasized as disciplines of physiology in medical courses. However, sufficient knowledge concerning functions of the blood; production and flow of lymph; formation and actions of digestive secretions; secretion of milk, urine, and sweat; physiology of respiration and animal heat, had accumulated to fill one of the two large volumes of Schäfer's textbook (2). While modern neurophysiologists would undoubtedly characterize as "limited" the knowledge of the central nervous system of 1900, it had nevertheless developed to such a degree that many neurologists of today base their diagnoses of nervous diseases essentially on information available at that time. The main ascending and descending tracts of the spinal cord were known, and the effects of lesions involving them had been established. Many characteristics of reflex cord reactions had already been determined by Sherrington through use of mammalian spinal preparations. The effects of various cortical lesions had been investigated experimentally, the motor areas of the cerebral cortex had been mapped in the dog, monkey, and in at least one anthropoid ape. Epilepsy had been induced by strong cortical stimulation, and aphasia assigned to Broca's area. Despite conflicting opinion regarding cerebellar functions, Sherrington's summary in Schäfer's textbook (2, p. 918) has a familiar modern ring: "It (the cerebellum) preponderantly helps to secure coordinate innervation of the skeletal musculature, both for maintenance of attitude and execution of movements." However, it must be admitted that our knowledge regarding

the functions of the ductless glands and metabolic processes was sadly deficient.

THE FIRST DECADE

I propose now to relate some earlier incidents and accidents that led to my adoption of physiology as a career and to draw such morals and conclusions as seem apropos. Decisions to enter a given profession are not based solely on inborn instincts; somehow, somewhere, sometime, a seed of interest must be planted in fertile soil. If properly nurtured and watered it may sprout into a fervor for the selected vocation; but it can grow into a sturdy plant that blossoms and bears fruit only through continued fertilization, spraying, and pruning. My interest in physiology as a science was not awakened by lectures or reading connected with regularly scheduled courses but through an educational experiment conceived by Lombard in 1902. The experiment consisted in assigning to each group of two students a research problem to be carried out during the last two weeks of a laboratory course. My partner and I were to investigate the debated question, whether the knee jerk is due to reflex excitation or to direct stimulation of the quadriceps maintained in reflex tonus. Of course, little progress was made during the short time available, but, my curiosity having been aroused, permission was given to pursue the quest independently in the evenings and on week ends. A new and simple method for inscribing an isometric contraction of the quadriceps, by the same system that recorded the tap, was devised. The technique is still being used in my laboratory courses for medical students. The results obtained agreed with observations of British physiologists, namely, that, available data being utilized, the interval between the tap and the start of contraction seemed too brief to permit impulses to travel over a reflex path. While these investigations were being pursued, Cushny granted me the privilege of assisting him in his experiments on free afternoons. My duties consisted largely in smoking drums and in cleaning up after the experiments. The stipend was nil, but the recompense for these services was large, for it afforded the opportunity to learn how a great experimenter observes, ponders, and deducts from his observations; for Cushny, as history records, was a pioneer in basic physiology as well as in experimental pharmacology. During this period of immaturity I was already beginning to classify masters of physiology as of two kinds: (a) those like Lombard, who delighted to design new apparatus, maintain the old in prime condition, and test each appliance as to its merits and efficiency, but who failed to make extensive use of such apparatus in experimental work; and (b) those like Cushny, who were content to employ relatively simple equipment, but who were active experimentally and had the vision to formulate research programs of signal value. Since both of these attributes are important, trainees should from the outset endeavor to develop both of these talents equally.

My parasitic association with laboratories of physiology and pharmacology could not help influencing my future inclinations. Lombard's attributes of neatness, precision, and manual dexterity—all had lasting synaptic aftereffects. The opportunity of watching investigators at work proved a

great treat to a young individual. During subsequent years, I have often had opportunities to witness experimental procedures in other laboratories. I have tried to profit from observations of good techniques and equipment and to avoid careless practices and habits noticed in others. Indeed, I have learned to assess scientific reports as much by an investigator's technical habits as by the actual data and deductions reported on the printed page. As Ludwig stated, "Die Methode is Alles," or, as phrased by Flourens, "Tout dans les recherches experimentales, depend de la methode, car c'est la methode qui donne les resultats." The moral to be drawn from my experiences would seem to be that, in order to evoke a research interest in predoctorate or neodocorate students, one should expose them as much as possible to experimental work in progress within a department. We oldsters prate a great deal about the failure of medical education to provide an adequate number of candidates for careers in basic sciences. At the same time, there seems to be greater insistence upon a medical training as a background for professorial appointment in medical schools. In a measure, we have only ourselves to blame for this lack of interest among medical students. Only exceptionally are medical students urged to witness experiments in progress; all too rarely are those who display some signs of interest invited to help in a minor way. Furthermore, there seems to be an increasing tendency to segregate research and teaching in separate rooms, floors, or divisions; the trend should be rather toward a building arrangement in which the student laboratory can be approached only through research quarters and a departmental library.

To return from this digression, for which I make no apology, I shall relate an even more decisive incident that affected my career. At the beginning of the junior year in medical school (1903) it was my considered plan to engage eventually in the practice of obstetrics and pediatrics. This program was destined to be upset by the resignation of the only instructor in the department of physiology and by the inability to replace him, as a result of which I was practically drafted to accept a half-time post as student assistant. Parenthetically, it is my considered judgment that in 1903 there were fewer physiologists relative to the positions available than at the present time. During this period of student assistantship, which consisted chiefly in aiding in the conduct of laboratory work, time was found to engage in a research on the innervation of the cerebral vessels. A new approach to the problem was found through perfusion of a completely isolated brain, and, when the 18th annual meeting of the American Physiological Society was held at Ann Arbor in December of 1905, it was possible to demonstrate satisfactorily that epinephrine constricts the cerebral vessels. The actual demonstration brought the realization that one can detect an aptitude for research—or its lack—more convincingly by the reactions of a critical audience than by any aptitude test yet designed. If I sensed opinions correctly, I had passed the test. Attendance at the meetings of the American Physiological Society also afforded a grand opportunity for gaining an initial acquaintance with many leading physiologists and for understanding how physiological advances are accomplished. Vivid recollections remain of the demonstration of

heart block by Erlanger, the registration of ventricular volume curves by Y. Henderson, the measurement of renal blood flow by Brodie, and the debate concerning the myogenic or neurogenic origin of the heart beat which ensued after Carlson's paper on the *Limulus* heart. All of these demonstrations were soon to have far-reaching effects on the interpretation of cardiac and vascular physiology. Younger persons who seem to display an interest in physiological work should be encouraged to attend meetings of this sort and should be assured that the outlay of money required is well invested. In my case it caused the seed of physiological interest to sprout, and the resolution was made to enter physiology as a career provided an opportunity arose. At that time, fellowships of which one could avail himself for entry into basic research were nonexistent. Opportunity arose only through attainment of an academic appointment in which teaching was emphasized and research was regarded as a sort of hobby. Fortunately an instructorship became available in 1906 because Lombard had finally convinced the regents that proper laboratory instruction for 120 students during three fourths of the academic year required an instructor in addition to a professor and two student assistants. Despite a considerable teaching load, I found time for investigations on the innervation of coronary and pulmonary vessels.

The years of my instructorship coincided with a period during which physiology began to challenge the claim of pathology as the foundation of clinical medicine. It was likewise the period of therapeutic nihilism and of faith that most diseases are self-curative through natural compensatory processes. These trends influenced me to become interested in more practical experimental problems, such as the compensatory mechanisms of hemorrhage. I began to appreciate, however, that the pressure recorders available at the time were not adequate to give correct answers to dynamic problems. Optically recording apparatus, such as had recently been designed by Otto Frank, was obviously required. Speculation began to take form as to ways and means by which an experience in the Munich laboratories might be realized, but the answer was not obvious.

During the academic year 1910 to 1911, it was my good fortune that an opportunity arose for gaining executive experience necessary for the conduct of a department. I have since regarded this as a fortunate incident, for the lack of administrative experience may have been contributory to the deflection of promising investigators from research after assumption of professorial duties. A sabbatical leave of absence granted Professor Lombard was the cause of my appointment as acting director of the department. The integration of administrative responsibility, teaching, and investigative work proved quite a thrill. A bold didactic experiment was instituted in which basic physiology was correlated with its clinical application. Such emphasis on the application of physiology to clinical medicine—without sacrifice of basic biochemical, biophysical, and mathematical aspects of the pure science—was developed further after my appointment in Cleveland. A calendar was worked out by which each member of the staff could plan some free time for research in rotation with teaching. At the close of the year an investigation by a member of the staff merited publication. At that time a tradition

or code of ethics had been handed down from Ludwig through his pupils that a department head should not allow his name to be added to a paper by a younger man, even though he might have outlined the work, participated in the experiments, aided in the interpretation of results, and finally, might be largely responsible for the manuscript. I followed this principle then and have continued to do so during my entire career. The current practice of placing the name of a superior as coauthor of a research, especially one in which he has taken little or no part, always appeals to me as useless, unfair, unjustifiable, and, in some instances, selfish.

Unfortunately, success often leads to megalomania. I did not escape it. During the middle of my administrative year confidence grew that I was quite ready to direct a department. Therefore, when two offers of professorships were received, an inflated ego tempted me to accept. In the first case, it was fortunately my privilege to discuss the matter with Dr. Huber, who happened to have Dr. Mall as his guest. Mall, when asked his opinion, replied, "I know nothing whatsoever about you, but, if you are good, the school is not good enough for you; if you are no good, the school is too good for you." Thus, one temptation was avoided. In the second case, I showed to Professor Novy a telegram, offering me a chair in physiology. After a quiet reflection, his answer was, "You are too young to be sitting in a chair; wire back concerning the status of their laboratory stools." I have always been grateful for these sound counsels. I would recommend that young investigators resist acceptance of positions in which advancement is apparent rather than real. The long view should always consider changes only on the basis of opportunity, never solely for the attainment of a better emolument or title. Many a promising career has been wrecked by failure to observe these rules of safety.

The academic year ending in 1911 terminated my fruitful connection with the Department of Physiology at Ann Arbor. Such an association for nearly a decade necessarily served to keep me abreast of the constant advances of that period. It is, therefore, the prerogative of an oldster to recount, and perhaps embellish a bit, the progress that to him seemed important during this decade.

The evolution of new physical principles and techniques and their prompt application to biological problems by Arrhenius, Bayliss, Bohr, Bottazzi, Hamburger, Wo. Ostwald, Jacques Loeb, and others, gave direction and purpose to the study of general physiology. Many of these investigators and others still to enter the field extended their work into the next decade. Thus Loeb, having rounded up his chemodynamic studies in a brilliant monograph which emphasized his mechanistic theory of life (29), devoted his later years to studies of colloid chemistry (30). Of great biological as well as practical importance during the first decade were Landsteiner's discovery of blood groups (1901) and Carrel's development of methods for vascular anastomosis and transplantation of tissues (1902). The physical and metabolic processes by which glands respond specifically to certain aliments [Pavlov (31)] were thoroughly studied by Bayliss and Starling (33). The

manner in which food is moved through the alimentary tract was greatly clarified by the use of roentgen rays by Cannon and others, and the roles that intrinsic and extrinsic mechanisms play were elucidated by Bayliss and Starling (33). As an outgrowth of his diuresis experiments, a "modern theory" of urinary secretion was formulated by Cushny which added to Ludwig's view the role of colloid osmotic pressure for glomerular filtration and the process of selective absorption by tubules (34).

The invention of the respiration calorimeter by Atwater (1904) offered great promise of future developments which were realized in later years by Benedict, Lusk, Du Bois, and their respective pupils. The headway that had been made by 1906 is summarized in Lusk's monograph (35). He submitted hitherto accepted theories to criticism and altered many of our concepts. Looking back, however, it seems that the experimental results had been pushed somewhat beyond available knowledge of basic organic chemistry. This was true despite the fact that it was an era of great advance in physiological chemistry. For example, Emil Fisher was engaged in studying the building stones of protein and had succeeded in synthesizing a polypeptid in 1903 and a whole protein molecule containing eighteen amino acids in 1907. Lusk's studies on phlorhizinized dogs were basic to interpretations of the process of gluconeogenesis and carbohydrate utilization. However, the significance attached to G:N ratios was to be challenged in years to come. At the same time, Macleod (36) was studying experimental glycosuria from various angles and thus gained the experience necessary to give direction and purpose to metabolic studies that arose immediately after the discovery of insulin (1921). Among the vital concepts enunciated in 1905 to 06 were those of *luxus consumption* by Chittenden (37), of exogenous and endogenous metabolism by Folin (38), and of the role that factors of safety play in animal economy by Meltzer (39).

The outstanding contribution in the field of endocrinology was probably Starling's concept of hormones. This developed out of observations that the entry of chyme into the duodenum excites pancreatic secretion through dispatch of a chemical messenger called secretin (33, 40). The new information, obtained through injection of extracts from ductless glands, from their surgical removal, and from observation of patients exhibiting glandular disorders, gave increasing evidence of their great importance in the control of body functions, but it was too indefinite to enable one to construct pictures of the *modus operandi* of these glands. Opinion had crystallized that the thyroid and parathyroid glands have separate functions. The idea that the increased formation of ammonia might be responsible for the tetany which follows parathyroidectomy was short-lived; but the demonstrations of MacCallum and Voegtlin that this symptom can be abrogated by injection of calcium solutions proved very valuable in later years.

The advances realized in various fields of the circulation were accomplished through investigations of basic phenomena, through inventions of new apparatus, and through the correlation of physiological studies with clinical applications. Carlson's demonstration of a neurogenic origin and

transmission of impulses in the *Limulus* heart (41) were soon shown to be inapplicable to the hearts of amphibia and mammals. The discoveries of nodal and conducting muscular tissue in previous eras, supplemented by new studies of impulse initiation and conduction, gave incontrovertible support to the myogenic theory (42). The physiological interpretation of graphic recordings of the pulse enabled Mackenzie to give physiological interpretations to many of the common irregularities (43). Additional experimental studies by Erlanger and Cushny elucidated the phenomena of heart block and atrial fibrillation, and their discoveries soon proved valuable in clinical diagnosis. The foremost step in the decade was the invention in 1903 of the string galvanometer by Einthoven (44) and his prompt application of this new tool to the study of physiological and clinical problems (45), for Einthoven was another rare scientist who was able to apply the combined talents of a mathematician, physicist, physiologist, and physician to the field of physiological investigation. The discerning mind of Thomas Lewis immediately envisaged the great strides that could be made in the field of clinical cardiology through correlation of electrographic phenomena in patients and experimental animals. By the end of the decade Einthoven's work had been enormously extended, both in physiological and clinical fields (46, 47). The design of optically recording manometers by Otto Frank, and of the technique for registering volume curves by Yandell Henderson, supplied a new approach to hemodynamics. However, use of these appliances was largely restricted to the hands of their designers.

During the first decade of this century the principles for measuring human arterial pressure and for the proper design of instruments for this purpose were practically perfected to the stage in which they exist today. The inherent errors in previous techniques for determining systolic pressure and in the sphygmomanometer of Riva Rocci (1896) and Leonard Hill (1897) were corrected through physical and experimental studies by von Recklinghausen and Erlanger. They also established oscillatory criteria and designed apparatus for the measurement of diastolic pressure. Erlanger and Hooker analyzed the hemodynamics and significance of pulse pressure and suggested that the product of pulse pressure and heart rate is a fair index of cardiac output. Impetus was given to the clinical practice of determining arterial pressures by the publication in 1904 of Janeway's stimulating monograph (48), which also summarized current knowledge. The auscultatory method now generally used was actually described by Korotkov in Russia in 1906 but, owing to latency of translation, remained unknown to us for many years. Incidentally, the validity of this criterion was not established until 1916 through Erlanger's experiments. Hooker and others introduced apparatus for the study of venous pressure in man. Improved forms of flowmeters were invented which allowed more exact measurement of blood flow through various organs. Burton Opitz was particularly productive in this field. The innervation of blood vessels and their control by agents acting directly and reflexly on the vasomotor center were comprehensively studied by many investigators in relation to other functions, among them secretion and shock. [For a partial review, see Bayliss (49).]

A new era of research in nerve physiology was begun. The perspicacity of investigators such as Lapique and Keith Lucas may be said to have prepared the soil for workers in subsequent years. The effectiveness of electrical stimuli was shown to depend upon parameters of intensity and time. The nature of excitation, the spread of the process over axons, and its transmission over neuromuscular junctions, were in their incipient stages of study. In the field of central nervous system physiology, the publication of Sherrington's classical monograph on the integrative action of the nervous system probably constituted the most significant advance (50). On the whole, further knowledge of the functions of the cerebrum, cerebellum, basal ganglia and spinal conduction pathways awaited the development of new techniques.

The methodology of physiological research was extended more generally also into the solution of practical problems, such as those that relate to exercise, high barometric pressures [as in caisson disease (51)], and other environmental factors on normal individuals. The term "applied physiology" thus came to have two connotations, namely, physiology as applied to problems of everyday life and as applied to problems of disease, also called functional pathology [Wright's *Applied Physiology* (16)].

THE SECOND DECADE

My personal experiences during the second decade date from an appointment as instructor under Lusk at Cornell University Medical College in New York City. The incidents surrounding my selection should perhaps be detailed for the benefit of younger physiologists, for they have implications even at the present time. I later learned from Lusk that I had been recommended by Howell because he had been impressed with the quality and manner of my presentations before the American Physiological Society. I mention this so that youngsters may be reminded that it is still common practice to select and promote physiologists on the basis of their public performances at scientific meetings. Perhaps this is also a suitable occasion to express parenthetically my gratitude for the interest that Howell always took in my welfare. It was he who urged my nomination to the American Physiological Society in 1907. Howell took special pains to introduce me to junior physiologists, as the result of which many lasting friendships developed. He was always gracious in making a few kind remarks in discussions of my papers, and, minor though my discoveries still were, he promptly incorporated them in successive editions of his textbook. The exhilaration of seeing one's work quoted in current texts is perhaps puerile but real. Authors of textbooks should keep this in mind as one way of encouraging younger investigators, especially since their small bricks contribute materially toward filling in crevices in the wall of physiological knowledge such as are usually left by epoch-making discoveries of established investigators.

Acceptance of a post under Lusk appeared to offer promise of at least three great opportunities: (a) association with a leading physiologist who had achieved a reputation for fostering research, both in basic sciences and clinical fields, and who, though not himself a medical man, had exerted a profound influence on clinical medicine in New York City; (b) membership in a

department with a light teaching load which thereby could be organized so that two-thirds of the academic year was available for pursuit of research; and (c) venture in a new field of training, namely, that of nutrition, in which Lusk and his group were masters. The last of these had an immediate appeal, since further progress in circulatory studies appeared temporarily blocked by the inadequacy of available recording apparatus, whereas use of respiration calorimeters seemed more likely to yield sound information on important problems of nutrition. It was therefore somewhat disappointing to learn upon arrival in New York that Lusk had other ideas. Since research on metabolism was already in progress, he desired to broaden departmental activities by encouraging research in circulation. Nevertheless, the metabolic atmosphere created by Lusk and Murlin could not fail to diffuse into the room devoted to circulatory studies. However, it was proper and necessary that I should fit into the scheme of departmental organization and make plans for continuing my former line of research. Others in similar situations have probably found that such adaptations are not always accomplished without some feelings of frustration. However, various unpredictable incidents or accidents usually solve the problem, provided the newcomer is alert enough to make use of them. I was fortunate in becoming acquainted with H. B. Williams, who, after a recent visit to Einthoven's laboratory, was reduplicating the Leyden instrument at the College of Physicians and Surgeons of Columbia University. Williams was loaded with information regarding the theory and construction of string galvanometers and the physical principle for eliminating extraneous mechanical and electrical vibrations. He was always willing to talk on these subjects, and I became an equally eager listener. In fact, except for Einthoven's visit in Cleveland in 1920 and my reciprocal visit with him in his home and laboratory, my knowledge of electrocardiography stems from my stimulating conferences with Williams. However, since he was presumably planning to employ the string galvanometer in physiological studies, and since Meek and Eyster in our country already had a decided start in applying this useful tool to cardiac problems, I hesitated to press for the large funds required for the acquisition of such an instrument. It was my privilege, however, a few years later to procure one of the first three string galvanometers constructed according to specifications of Williams in the shops of the College of Physicians and Surgeons.

My yearning to serve an apprenticeship under Otto Frank in Munich in order to gain a more intimate familiarity with new types of apparatus designed for dynamic studies reached early fruition unexpectedly. Lusk, having been associated with Frank in Voit's laboratory, found no difficulty in arranging the opportunity. He also arranged a leave of absence, with salary, during the last portion of my first year, a generous and unusual procedure at that time, and in addition made available the sum of \$500 for the purchase of necessary new apparatus, presumably a personal donation.

The foregoing incident is related because many earnest younger physiologists must find themselves in a similar quandary as to the procedure by which training and special techniques may be acquired under masters in the

field. They will generally find that their chiefs will welcome frank discussion of well considered plans and will offer to assist them in their fulfillment, even though this may involve temporary deterioration of departmental efficiency. Fortunately, many agencies now exist for the encouragement of such development. However, it may be expected that those who enjoy such advantages will have a sense of obligation to utilize the training obtained for the advancement of physiology or cognate sciences.

My training in the Physiological Institute at Munich, coupled with privileges extended by Garten in Giessen, opened a new outlook on the construction and proper employment of optically recording instruments. Otto Frank belonged to that group of great physiologists who concentrated more largely on the development of new tools than on their utilization in experimental work. An association with him therefore afforded the opportunity needed to gain a firsthand acquaintance with his newly developed apparatus and to understand the principles of its construction. The latter proved highly important, for repeated modifications in the design of Frank's instruments were required before they were applicable to the experimental and clinical problems I had in mind. The first application of optically recording manometers was made to studies of the dynamics of valvular lesions and hemorrhage. However, a short period of such investigation made it evident that an analysis of results required more detailed knowledge of normal mechanisms that we had at that time. Therefore, the following few years were devoted largely to acquiring this needed information. Returning to the study of so-called practical problems, such a need for more basic research has arisen again and again. Thus, whereas it was my avowed aim to contribute chiefly to the solution of clinical problems, most of my investigations have reverted to basic fields. While our lack of fundamental knowledge is disconcerting when it crops up during investigations of practical problems—either in the laboratory or clinic—it is comforting for physiologists to know that not all basic research is at an end.

Having gained some experience in hemodynamic studies, both in animals and hospital patients, I decided in 1915 to incorporate the current knowledge of the circulation in health and disease in a monograph (52). In this connection the observation may be made that it is a duty as well as a privilege for experienced investigators to present occasionally an analysis of the subject in which they are proficient in the form of monographs and reviews in order that others may become acquainted more easily with recent advances in the subject.

Younger investigators derive great benefit from frequent contacts with active workers in their communities. In general, such opportunities for repeated exchange of ideas increase with the number of research centers in a circumscribed geographical area. New York City during 1911 to 18 afforded splendid opportunities for development of intimate acquaintance with one's contemporaries and their work. Also, the "Meltzer Verein" (the Society for Experimental Biology and Medicine) which then held its meetings in different laboratories of the city, served as a good mixer, while the Harvey Society

brought distinguished guests as lecturers. In this connection, the observation may not be wholly gratuitous that the value of a lecture depends less on the summary of current knowledge than on the stimulation of the listener to delve somewhat deeper into the subject in the quiet of the library. Truly, a good library is also an invaluable asset for the development of an investigator.

Despite the many advantages of an academic career, the disparity between salaries and cost of living and the small chance of becoming an incumbent of one of the few available chairs impel many a younger scientist to accept a more remunerative nonacademic post. I did not escape consideration of such a deflection to commercial fields or medical practice. Lusk's advice to me, which I have passed on to succeeding generations, was: "Hold off until forty. Then, if not in a favorable academic position with tenure for life, consider such a change carefully." I commend this rule to perturbed younger physiologists.

With our entry into World War I the administrative and teaching functions of a department again devolved upon me, and the time available for research was devoted to experimental studies on shock. Unfortunately, most of my hemodynamic studies tended to confuse rather than clarify the issues. However, the privilege of attending many group conferences of a national committee on shock under the chairmanship of Howell proved of great personal benefit. Among other benefits, it caused previous acquaintances with such scientists as Hooker, Macleod, Yandell Henderson, and Torald Sollmann to grow into lasting friendships. In particular, Sollmann's sagacity, discriminating judgment, and happy optimism proved invaluable in succeeding years. Later it was my privilege to join Major Peabody in the U.S. Army Hospital at Lakewood, N. J., in efforts to elucidate the nature of functional disturbances of the heart in soldiers. Unfortunately, no great headway was made in the real solution of the problem, either by our group at Lakewood or by that of Thomas Lewis in the Military Heart Hospital at Hampstead, England (53). However, the brief association with Peabody gave me an insight into the trend that modern medicine was likely to assume and the part that the physiological study of patients was destined to play. The manifold influences that Peabody exerted on the future trends of scientific medicine were obvious to us during the Lakewood association. He had, for example, the ability to surround himself with a remarkable group of interns and assistants, such as Clough, Stroud, Sturgis, and Wearn, each of whom has attained pre-eminence in the field of medicine. When it appeared clear in the fall of 1918 that the war would soon terminate, I felt no compunction in accepting a professorship at Western Reserve University. The second decade of the present century was now nearing an end.

Among the advances in physiology that impressed me most during this decade, I should perhaps mention first the great strides in explaining physiological phenomena in biochemical and biophysical terms. The publication of Bayliss' book on general physiology (10) and that of Burns on biophysics (54) excited the greatest interest. These authors defined the scope of subjects

that can be included in these respective areas. The monograph of Lucas (55) revealed the new thinking with regard to the nature and passage of the nerve impulse. Hasselbalch, Michaelis, and Mansfield Clark contributed in numerous ways to the application of pH measurements in biological systems. L. J. Henderson formulated the chemical reactions by which pH in buffered solutions and acid excretion of the body maintains its constancy (56). His conceptions were extended by Van Slyke's procedure of determining the degree of acidosis and of available alkali reserve in terms of carbon dioxide combining power.

The concept of the glomerular filtration of dilute urine was placed on a firm foundation by a variety of experimental procedures [Cushny (34)]. The demonstration that glomerular capillary pressure is regulated by differential effects of stimuli on afferent and efferent vessels and that an intermittency of glomerular flow occurs in the frog's kidney removed some of the weighty objections that had been raised against the filtration hypothesis (57). In 1912, Ambard and Weil suggested an equation which related the rate of urea excretion to blood urea in a dynamic sense. After additional studies of McLean, Addis, and Van Slyke, the volume of blood cleared of urea by one minute's excretion came to be expressed as urea clearance (1921). The far-reaching importance of this methodology in the assessment of renal function could not be appreciated until the later decades of this century. Early in this decade it was my privilege to observe a demonstration by Abel and his colleagues of a vividiffusion apparatus which, though primarily designed to study the absorption of amino acids, unquestionably suggested the construction and use of artificial kidneys in the present era. Meanwhile, Sabin's study of the growth of the lymphatic system (58), establishing the noncontinuity of lymphatic and tissue spaces, was destined to influence basic concepts of lymph formation and edema.

Renewed studies were made of the problem as to how chemical energy is converted to muscular work during contraction, but the chemo- and thermodynamic studies of muscle and nerve came to fruition only in succeeding decades.

The studies of Howell (59) gave us a clearer insight into the process of blood coagulation, the chemical factors concerned, and their reactions, but he could not realize at the time that the process would turn out to be far more complicated than his theory of coagulation implied. During this period the natural destruction of red cells by fragmentation rather than by hemolysis was demonstrated by Rous, but the life span of red corpuscles appeared to vary with the technique employed.

Continued improvements in gasometric apparatus and experimental procedures seemed to have proved conclusively [see Haldane (60), Barcroft (61), Krogh (62)] that the respiratory center is dominantly controlled through humoral mechanisms. The difficulties in such interpretations, which subsequently led to revision in our conceptions that other factors, including nervous regulation, are also important, occurred chiefly in later decades. For example, Gesell first proposed the hypothesis that the respiratory center

is regulated by intracellular acidity in December, 1922. The suggestion of Bohr (1909), also supported by Haldane, that under certain conditions the pulmonary epithelium has a secretory power in transferring oxygen, was put to test by successive scientific expeditions to Pike's Peak (1913) and to Cerro de Pasco in Peru (1914). The problem appeared to be finally settled by Barcroft, who lived for six days in a low pressure chamber (1920). However, the problem continued to excite interest up to the present war, when it was again investigated by making use of significant improvements in technique.

In summary, it appeared that physiologists were ready to accept as the orthodox creed that physiology is only a special application of ordinary physics and chemistry (10, 21, 29, 63) and were inclined to regard any deviation from this creed as scientific heresy. Haldane, however, denounced such a conception and urged physiologists to view the organism as a whole and not to be carried away by mechanistic concepts derived from the studies of isolated tissues. He called the attempts to analyze living organisms as physical and chemical mechanisms a colossal failure and urged that the new physiology be regarded as biological physiology—not biophysics or biochemistry (64). My own considered reactions have always been that something may be said in favor of such a view, but not a great deal.

Progress in the study of metabolism proceeded in so many directions that any brief summary is necessarily inadequate. Many of the mysteries of the intermediary metabolism of fats, carbohydrates, and proteins were unraveled through development of new chemical procedures. Only a few high points that impressed me can be mentioned. Knoop's concept of beta oxidation of fatty acids (65) remained unchallenged. The fate of absorbed amino acids was elucidated (66). The grouping of amino acids as dispensable and indispensable for growth was realized in part. Gluconeogenesis and combustion of carbohydrates by tissues was intensively studied, particularly in relation to clinical, phlorhizin, and pancreatic diabetes. The mechanism of ketosis and the ketolytic products which prevented its occurrence under normal conditions were analyzed (67, 68). Investigators most intimately concerned with the study of diabetes had the feeling that the nature of the pancreatic hormone was on the verge of discovery, which actually eventuated in 1922. The mechanism of oxidation received a great deal of attention; new enzymes were discovered and new theories set up. However, the suggestion made by Ostwald in 1898, that oxidation can be expressed basically only in terms of electrical charges, was largely bypassed except by a few brave souls.

The study of respiratory metabolism in disease, begun by Benedict and Joselyn in 1910, received a great impetus through construction of a respiration calorimeter in New York and its utilization by DuBois and his associates. These studies yielded much information regarding human diabetes mellitus, typhoid fever, malaria, anemia, and cardiorenal diseases, and supplied a rational foundation for providing proper nutrition for patients with different disorders (69).

Of far-reaching importance in the future outlook upon nutrition was the

growing recognition that foods contain factors accessory to energy-yielding and tissue-building components and, particularly, Funk's designation of the missing accessory factor in polished rice as a "vitamin E" (1911). Exciting discoveries occurred in rapid succession. During 1913 to 16, McCollum and his associates discovered a growth-promoting factor in butterfat and eggs which they called fat-soluble A, distinct from the water-soluble component called water-soluble B in a diet producing beri-beri (70). During 1914 to 18, Hess (71) demonstrated the presence of a water-soluble vitamin C in fruits and tomatoes, deficiency of which led to scurvy. In 1919, Mellanby discovered that cod liver oil contains a factor, vitamin D, which caused marked improvement in experimental rickets. Only a few years later (1922), Evans and his associates located another vitamin (E) in wheat germ and lettuce leaves which was concerned with reproductive power and sterility. Thus, by 1922 vitamins A, B, C, D, and E had all been discovered, and a suspicion existed that B was composed of two elements, an antineuritic and a pellagra preventative component (Goldberger). The practical and clinical value of these discoveries quickly became apparent.

Outstanding advancements in the field of circulation were realized through the more general availability of string galvanometers and their employment by competent investigators with imaginative minds; the design of new forms of optical myographs, pressure manometers, heart sound recorders, and their employment both in laboratories and clinics; and the development of clever procedures by means of which the operation of the heart beat could be studied. The famed heart-lung preparation, which Starling once demonstrated to me during a visit to his laboratory, was among the latter.

An idea as to the breadth of the advancing front can be gained from a list of the circulatory problems attacked and at least partially solved. Knowledge was extended with regard to (a) the spread of the excitatory process over the atria and ventricles, (b) the nature of cardiac irregularities, (c) the relation of electric and dynamic cardiac events, (d) the fractionate character of atrial contractions and their dynamic importance, (e) the details of sequential phases of the cardiac cycle, (f) the forces concerned in closure of cardiac valves, (g) the changes in sounds in their transmission from the heart to the chest wall, (h) the factors which determine the intensity of heart sounds, (i) the precise timing of murmurs in valvular heart disease, and (j) the control of the pulmonary circulation (72). Advances in the dynamics of the heart beat included (a) the conception and determination of the effective atrial pressures; (b) the reactions of the ventricles to changes in initial tension, initial length, aortic resistance, and heart rate, as manifested by alterations in stroke volume and modes of ventricular filling and ejection; (c) the interpretation of cardiac tonus and its role in cardiodynamics; and (d) the formulation of Starling's law of the heart and the author's concept of the autoregulation of cardiac compensation and decompensation (73, 74, 75). Studies on cardiac metabolism, coronary flow, and capillary circulation remained in incipient stages of the tremendous progress yet to be achieved in the next decade (76, 77, 78).

The second decade also saw the birth of the new speciality of clinical cardiology, which also included studies of peripheral blood flow in vascular and cardiac disorders (Hewlett, Stewart). Clinical problems such as dynamic effects of cardiac irregularities and valvular insufficiency were returned to the laboratory for more basic study. The circulatory changes produced by anoxia and shock were studied intensively both in animals and man. At the close of the decade it was the consensus that the decline of arterial pressure in shock is caused by reduction in circulating volume, occasioned either through loss of fluid or increase in vascular capacity [Bayliss (79)]. It was believed that capillaries dilate and become more permeable through release of histamine-like substances (80) and that these processes lead to progressive reduction in venous return and cardiac output (81, 82).

The smog that had enveloped the ductless glands began to lift a little. The rate of progress can be judged by comparing the monographs of Biedl (83) and of Sharpey-Schafer (84) with surveys of the subject in the Harvey Lectures of 1923 to 24 by Biedl, Marine, Abel, and H. M. Evans. In 1916, Sharpey-Schafer (84) proposed that internal secretions be designated as auto-coids, which include hormones that excite and chalones that inhibit. The headway during this decade may be indicated by a few sketchy notations concerning some representative endocrine organs: it had been established that the adrenal cortex and medulla have separate functions, but, aside from an apparent relation to sex organs, the function of the cortex remained obscure. Macleod (12) in 1918, for example, made the frank statement: "Some facts indicate that it has other functions." It was well known that the medulla elaborates a principle, epinephrine, the secretion of which is under the control of nerves. Researches of the period were largely concerned with the biological assay of epinephrine in the blood and led to the controversy between Cannon and Stewart as to whether the medulla had an emergency function or none at all (85, 86). No conclusive evidence existed at the close of World War I that the adrenal medulla is implicated in shock.

The outstanding contributions to the physiology of the thyroid consisted in the isolation and physiological study of thyroxin by Kendall (87), and in the demonstration by Marine and his associates (88) that iodine is important in determining thyroid activity and in the prevention of colloidal goiter. Rival theories developed, holding that the symptoms following parathyroidectomy are due to (a) guanidine intoxication (Noel Paton) or (b) to calcium deficiency (MacCallum and Voegtlin). The problem was soon to be settled by Collip's discovery of a parathyroid hormone (1926).

Considerable clarification regarding the functions of separate parts of the pituitary resulted from the clinical and experimental studies of Houssay (89) and Cushing (90) and their pupils. It appeared to be the consensus that the anterior pituitary principles controlled the growth of bones and musculature and the development of the sexual organs, while the principles of the posterior lobe are concerned with regulation of urinary secretion and the metabolism of carbohydrate and fat. Cushing visualized the pituitary gland as the conductor of the endocrine orchestra, a concept of master function which is retained to the present day.

The techniques of tissue culture and experimental cytology were developed and an incipient attempt made in the biostatistical analysis of experimental results (Pearl). During this period, Cannon (91) philosophized on the meaning of his many experiments in a monograph dealing with the bodily effects of fear, hunger, pain, and rage. Carlson (92) restudied the phenomenon of hunger in its broad biological as well as practical aspects.

A few general remarks concerning physiological advances during World War I shall conclude this narrative. When a nation enters into a modern war it invariably finds itself unprepared to meet new emergencies created by unforeseen developments and construction of deadlier weapons. This applies not only to military equipment and tactics but also to professional skills and scientific knowledge. Consequently, new knowledge must be acquired rapidly and applied to military situations. The field of research into which physiology fitted during World War I covered, among others, problems of food supply for soldiers, the nature and treatment of hemorrhage and shock, the effects of and treatment of poisoning with lethal war gases, the results of high explosives upon the ear and central nervous system, and the problems associated with new development of aerial warfare. Altitude physiology became an acute subject because a military advantage was gained by the aviator who could climb above his adversary and choose the moment of attack. While aerial combats took place at comparatively low altitudes at the beginning of World War II, planes capable of ascending as high as 15,000 to 18,000 feet were developed before its close. Our preparedness in the field of altitude physiology rested largely on the monumental monograph published by Paul Bert in 1878 (93), which, incidentally, was regarded so highly as an old testament that a translation was ordered during the last war by Hitchcock (94). A new testament of facts was also available as a result of additional studies made by various expeditions to mountain peaks. The knowledge of nitrogen embolism derived from studies of sudden decompression of divers was as yet of no great importance, since fighting planes could scarcely attain an altitude of 20,000 feet. The chief problem for physiological investigators, therefore, consisted in testing candidates for the air service with regard to their response to low barometric pressures in decompression chambers and to low oxygen mixtures breathed from spirometers. The practical problem that confronted the Mineola Research Laboratory during this emergency was to determine the effects of rapidly decreasing oxygen tension on the heart rate, arterial pressure, heart sounds, muscular coordination, and psychic reactions of persons rated as good, average, and poor, and to systematize and apply these standards on a large scale in flying fields in France. The work accomplished by this laboratory during its brief existence (95) was not only of immediate military value but also of immense significance in expanding our physiological knowledge and, most important, in stimulating interest in aviation physiology as a specialty. This led eventually to the creation of a number of aviation research laboratories in various institutions and in special governmental laboratories under the supervision of the Civil Aeronautical Authority (Medical Science Station, C.A.A., Kansas City, Missouri, 1938); the Army (Wright Field, Dayton, Ohio,

1934; School of Aviation Medicine, Dallas, Texas, 1939); and the Navy (School of Aviation Medicine, Pensacola, Florida, 1939).

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PERMEABILITY

BY H. BURR STEINBACH

Department of Zoology, University of Minnesota, Minneapolis, Minnesota

INTRODUCTION

To the reviewer's knowledge, no notable new concepts have been outlined nor new techniques developed for the period July, 1948 to June, 1950, relating to permeability. However, there has been a rather marked shift in emphasis over the past several years and an attempt will be made to note and evaluate major trends. While many biological periodicals have been consulted, important omissions most probably will be noted and for these the reviewer apologizes in advance. The reviewer has arbitrarily omitted mention of preliminary short reports and abstracts, even though they may have appeared to contain material of considerable interest. In a field so difficult of interpretation as permeability, it is felt that nothing short of a complete report warrants critical review. A number of references to literature on permeability were included last year by Kopac (1) in his review of protoplasmic structure.

The years under review were marked by the loss of two men who made notable contributions to our basic knowledge of permeability problems. Leonor Michaelis carried out, in addition to his many other activities, the original detailed investigations of dried collodion membranes which have proven so useful as models for some cellular phenomena. August Krogh, likewise a scientist of varied achievements, spent many of his last years studying active ion uptake by whole animals as well as by cells and tissues. He pioneered in this work which has recently engaged the attention of an increasingly large number of competent investigators.

The reviewer recommends that the stimulating discussion in the first part of the review by Teorell (2) be re-read periodically by all students of permeability. Insofar as it is possible, the terms used in this review will conform to those defined by Teorell.

Teorell, in his 1949 review (2), stated that it was his impression that there was a considerable decrease in the number of published papers dealing with permeability, as compared with previous periods. This impression is shared by the present reviewer and is borne out by the listings of "Permeability" as related to living systems, in *Chemical Abstracts*, 32 items being listed in 1949 as contrasted to 46 in 1941 and 88 in 1937. This does not reflect any diminution in interest in problems of exchange of materials between living units and their environment, but rather a recognition that such processes are best studied in terms of other general activities of organisms such as assimilation and nutrition, rather than as phenomena, ends in themselves. Observations relating to permeability are no longer most apt to be found in papers using the specific term in the title. Thus it becomes even more

important to refer the reader to chapters dealing with secretion, mineral nutrition of plants, absorption, and structure of protoplasm, as well as to those reviewing activities of special organs such as kidney, skin, placenta, liver, and so forth. Also relating to the wide dispersion of papers containing material of interest to students of permeability is the fact that reviews of the subject tend more and more to reflect the special interests of the reviewers. The present discussion is no exception to the trend.

GENERAL COMMENTS

If a given substance can be shown to pass through a boundary, the boundary is said to be permeable to that substance. The term "permeability," in a strict sense, means just this property. Nothing is implied about the mechanisms involved in the transfer although, in the past, permeability studies have been used to argue for free diffusion in pores, diffusion by solubility in a phase boundary and so on.

In a general way, it can be said that much work on permeability in past years has been done from an "equilibrium" point of view, interest centering around considerations which assumed relatively static, inert conditions for the cell, especially the cell surface. This point of view was admirably summarized by Davson & Danielli some years ago (3). A cell or tissue was placed in a solution of, say glycerol, and either rates of penetration of glycerol or volume changes of the cells were measured. The results could then be described in terms of the usual diffusion equations and constants assigned, not always, unfortunately, with due regard for variables included in the "constants."

More recently, there has been an increasing tendency to recognize the living cell as an active part of an open system. Perhaps the point of view can be best explained by quoting from a paper by workers whose approach to problems of cell permeability is refreshingly untouched by traditional words (4). "... the dominating factor in cell permeability is not any inherent and constant physical property of the cell wall, like porosity or lipid-sieve structure, but a mechanism dependent on the supply of energy." The reviewer feels that the general philosophy expressed will continue to prove useful, provided, of course, that static aspects of the problems are not ignored.

Isotope tracer studies have emphasized some of the discrepancies in the use of the term "permeability." Prior to the advent of these agents, only total changes in amounts of substances in cells could be measured by direct analytical procedures, or inferred indirectly as with experiments on volume changes. With isotopes, net changes and exchanges may be measured. For example, in the frog sartorius, the permeability of the membrane for sodium ions (free diffusion) is probably rather low, while the permeability to sodium, as measured by isotope exchange, is high (5). The inference is that the membrane, in addition to allowing a slight leakage of sodium ions, also has a specific exchange system which may not appear in conductivity measure-

ments and which does not lead to a change in total amount of sodium within the fibers and hence would not appear in analytical chemical studies. Especially with isotope studies, it is becoming increasingly important to specify conditions precisely and to recognize whether changes in total concentration or only exchanges are involved before comparing results with those obtained by other methods. Needless to say, it is also important to guard against injurious effects of radiations when radioactive isotopes are used. No papers dealing with this problem have come to the attention of the reviewer. Numerous useful discussions on applications of tracers to biological problems may be found in a recent symposium (6).

For many years it has been recognized that some substances, added to the external environment, first combine specifically with the cell surface and then may penetrate, turning up, apparently unchanged, in the inner protoplasm. Since this appears to involve incorporation of the externally applied substance into the structure of the living cell, the process can be thought of as assimilation and the propriety of designating the cell to be permeable to the substance in question may be doubted. There is an increasing number of papers whose titles read "Uptake of . . ." rather than "Permeability to" The case of phosphorus in yeast, as discussed by Spiegelman & Kamen (7), illustrates the situation. Tracer phosphate, added to the medium, is taken up by yeast in the presence of sugar. The process may be stopped by appropriate inhibitors. Kinetic analyses and isotope distributions among the various phosphate fractions lead to the conclusion that phosphate enters by combination at the cell surface, some of the entering material appearing soon inside the cell as inorganic phosphate. Thus orthophosphate, added to the medium under the proper conditions, appears as orthophosphate inside the cell and, according to definition, the cell is permeable to phosphate. On the other hand, a given molecule may have gone through many stages of identification with synthetic end products between the time it was first combined at the cell surface and the time it appeared in the interior as the same type of compound originally added to the medium. In a sense then, the cell never was permeable to orthophosphate; the compound appeared in the interior because it was assimilated, finally, and only incidentally, in its original chemical state. In similar fashion, calcium added to the medium is taken up by *Elodea* cells and then given off to form insoluble oxalates in the vacuole (8). By analogy with the phosphate story, it could be argued either that the cell was permeable to calcium or that the cell was impermeable to calcium but assimilated the element.

Ideally, it should be possible to discuss the uptake of materials by cells, or loss from them, either as a passive process taking place due to diffusion through a boundary or as an active process of assimilation and synthesis. The processes of the latter category must, of course, take place against a background of the simple driving forces of the former (chemical or electrochemical gradients) but involving such special mechanisms as to render the general definition of permeability almost useless. At the present time, how-

ever, the reviewer sees no alternative to adopting the very general definition of permeability, attempting to sort out mechanisms as work proceeds.

PERMEABILITY TO STRONG INORGANIC ELECTROLYTES

This heading is retained by the reviewer for want of a better designation, in spite of the probability that, in many instances, the penetration of cells by the ion-forming constituents of the medium may well be as non-ionized bound combinations. A discussion of exchange phenomena in general may be found in Ussing's review (9), and in the literature on salt uptake by plants (10). A monograph on ion binding in soils is informative and useful (11). The paper by Hodgkin & Katz (12) contains calculations regarding ionic conductance in the nerve membrane, and Katz assembles data on electrical characteristics of muscle and nerve (13). Danielli has written briefly on concentration of ions at interfaces (14). Nachmansohn (15) has reviewed problems of permeability as related to nerve function with special stress on movements of inorganic ions, acetylcholine and related substances, and the anti-cholinesterases.

Muscle and nerve.—Observations over the past several years, especially with radioactive isotopes, have confirmed the findings with analytical chemical methods that muscle and nerve are apparently permeable to all of the normal inorganic constituents of the environment (16). Sharp attention is thus focused on problems of specific ion transport mechanisms, in order to account for the normal ion distribution between cell and environment. Special interest has been aroused among electro-physiologists by the suggestion of Hodgkin & Katz (12) that the "overshoot" of the action potential may be explained in terms of marked alterations in permeability of the nerve axon to sodium.

Considerable attention has been paid to the sodium-potassium balance in muscle and nerve fibers (9). Levi & Ussing (5), after equilibrating frog sartorius muscles with Ringers' fluid containing Na^{24} or Cl^{38} , studied the time course of washing out of radioactive isotopes. Na^{24} left the muscle in a fashion suggesting a rapid removal from the interspaces and a slower loss from the fibers. Approximate half times for Na^{24} loss from fibers were 34 min. at 20°C . and 70 min. at 1°C . Cl^{38} apparently left the fibers at a faster rate. No effects of altered potassium concentration were noted on sodium or chloride movement. The authors, after consideration of energy requirements, conclude that Cl^{38} movement may be by simple ionic diffusion, Na^{24} most probably as specific ion exchange or transport in large part with small but unknown fractions of free ionic diffusion. Harris & Burn (17) have studied both uptake and loss of K^{42} and Na^{24} by sartorius muscles of the frog. Their paper contains an extensive treatment of methods of calculating permeability and diffusion constants in a system of interspaces and fibers. Average permeability values obtained were 3.4×10^{-3} cm. per hr.⁻¹ for potassium and 5.2×10^{-4} cm. per hr.⁻¹ for sodium. No effect of altered potassium concentration on either sodium or potassium permeability was noted.

Rothenberg (18) has reported on the uptake of Na^{24} , K^{42} , and Ca^{45} by squid giant fibers immersed in artificial sea water enriched with the appropriate elements. Uptake was measured by collecting extruded axoplasm after equilibration of the whole nerves and axons. "P" values calculated according to Krogh gave 1.25×10^{-3} cm. per hr. for potassium and 5.76×10^{-2} cm. per hr. for sodium as representative values. The precise significance of the constants is difficult to evaluate, however, due to an incomplete (10 per cent) exchange of K^{42} . Ca^{45} penetrated into the axons in a rather complicated fashion, first apparently accumulating and then partially leaving the fibers after longer immersion times. Electrical excitation increased the rate of Na^{24} penetration, as did x-ray irradiation. Anticholinesterases increase the rate of Na^{24} penetration and decrease that of K^{42} . Cocaine has no marked effect.

Keynes (18a) has reported on influx, outflux, and exchange constants for Na^{24} and K^{42} with *Sepia* axons. In resting nerve, the influx of Na^{24} is about three times that of K^{42} , and during activity, over 20 times. This provides direct evidence for the suggestion of Hodgkin & Katz (12) that sodium entry increases markedly, as compared to potassium, during excitation of nerve. It is perhaps worth noting that the ratio, influx Na/influx K, during activity, approaches the ratio for external concentrations of the respective ions.

Leakage of potassium from brain during anoxia has been noted by Dixon (19), from embryonic chick muscle during cooling by Wesson *et al.* (20) and from peripheral nerve by Fenn & Gerschman (21). The latter authors find a considerable increase in potassium loss during anoxia as compared to normal. Acetylcholine also increases potassium loss. Fischer (22) has found that potassium is lost and sodium is gained during atrophy of muscle, but only to a limited extent. In general, potassium loss parallels loss of extractable myosin.

An increased rate of potassium loss from muscle, nerve, and other systems, following exposure to anoxia and other conditions, has sometimes been interpreted as evidence for an increase in permeability to potassium. Great care should be exercised in making such judgments, since several factors are concerned with any rate of net movement of ions. Ions tend to move under the influence of a driving force defined as an electrochemical gradient (=chemical gradient and potential difference). In a normal resting muscle, potential differences balance chemical gradients nicely for potassium and chloride (2, 9). Any treatment tending, for example, to decrease the potential difference would automatically throw off the balance, resulting in a rapid net flow consistent with the chemical gradient. In addition, any alteration of a transport mechanism, for sodium for example, could cause net shifts in other ions according to their respective chemical gradients. It is thus very easy to have "false permeability changes" if any factor leading to normal distribution of ions is neglected. A change in driving force does not imply a change in permeability.

The interesting studies on sodium-potassium balance of insects have been

continued by Tobias (23). Shenk (24) has compared methods of chloride determination in muscle tissue and concludes that the usual HNO_3 digestion gives low values as compared to the Parr bomb method. Fleckenstein (25, 26) develops the novel suggestion that the primary source of energy for contraction of muscle resides in the osmotic pressure relationships of intra- and extra-cellular sodium and potassium, sodium normally being bound in an outer envelope. It is difficult to visualize the coupling of such a system to a contractile mechanism [cf. also (27)].

Feng & Liu (28) have investigated the effects of salts on amphibian nerve in an attempt to evaluate the permeability of the sheath to these agents. They conclude that the sheath is a real barrier to passage of inorganic components of the medium, a conclusion that is hotly contested by Lorente de N6 (29). The reviewer is of the opinion that the controversy illustrates very well the dangers of attempting to determine permeability to an agent by studying the physiological effects of the agent. The system under discussion by the several authors is very amenable to direct investigation.

While perhaps not of primary interest to the subject of permeability, attention should be drawn to the calculations of Hill (30) showing that diffusion, presumably of ions such as calcium, could be fast enough to account for the coupling of excitation and contraction in striated muscle fibers, provided that the whole cross section of the fiber need not be involved. In a later paper, however, Hill (31) concludes that during a single twitch the whole fiber does respond and hence there must be some inward transmission of excitation other than diffusion of ions.

As in prior periods, there have been numerous bioelectric studies, most of which are interpreted in terms of permeability to ions. The reader is referred to discussions of muscle, nerve, and bioelectric potentials for details. While membrane conductance and impedance measurements in general give direct evidence of permeability to ions, the reviewer feels that the usual resting potential studies can be related to permeability only with great caution. Wide variations in permeability may be demonstrated in artificial membranes with little or no change in concentration potential (32).

Multicellular membranes.—With the primary aim of studying active uptake and transport of ions, a series of investigations has been reported from the group in Copenhagen formerly headed by Krogh. Ussing (33) has reviewed much of this work, the major results of which will be mentioned under the heading ACCUMULATION AND ACTIVE TRANSPORT OF IONS. Ussing (34), using Na^{24} , shows that sodium flux from outside to inside of frog skin is much greater than in the reverse direction, the difference tending to be abolished by cyanide which causes a decrease of influx. Epinephrine action tends to equalize influx and outflux because of a differential increase in both. Barker-J6rgensen (35) finds a considerable increase in permeability of frog skin to both water and salt during moulting, together with increased salt uptake. A rapid increase in water uptake is noted in whole frogs upon exposure to low temperatures, followed by a slow increase which parallels an

increase in active salt uptake (36). Salt depleted frogs can take up salt from more dilute solutions than can normal animals (37). Linderholm (38) has studied ion permeability and electric conductivity of frog skin. Electrical permeability resistance (= DC resistance minus high frequency AC resistance) can vary widely with no change of net ionic outflux. A derived characteristic termed "reduced electrical resistance" does correlate over a limited range with ion flux.

Flexner, Cowie & Vosburgh (39) have summarized their studies relating to capillary permeability. Using Cl^{38} , Na^{24} , and DHO they conclude that the capillary wall of the guinea pig is 2.3 times as permeable to water as to sodium and chloride. Diffusion appears to be the predominant process concerned. Morel & Marois (40, 41) also note a rapid equilibration of Na^{24} between blood and tissue fluid.

A rapid exchange of Na^{24} and DHO across the placental barrier has been described by Flexner *et al.* (42) and Hellman *et al.* (43) in the human female and the guinea pig. Permeability increases markedly during gestation with water permeability always greater than that for salt. The rate of renewal of sodium in amniotic fluid is also very rapid (44). Placental interchange has been the subject of a review (45). Bárány (46) reports that the entrance of Na^{24} into the aqueous humor of the rabbit is independent of arterial pressure, thus indicating that ultrafiltration is not of paramount importance. The penetration of Na^{24} and chloride into cerebrospinal fluid has been studied (47).

A permeability of the gastric mucosa to hydrogen ions, as distinct from active secretion, has been demonstrated by Turner (48), who has shown that back-diffusion of the ions from the secretory side of gastric mucosa is probably a continuing process during both rest and activity. The rate of back-diffusion is a linear function of acid concentration gradient.

Flexner & Flexner (49) followed sodium and chloride changes in guinea pig cerebral cortex during foetal development and note that extracellular space (nonchloride) decreases sharply after about 40 days of gestation. At about that time, sodium in excess of chloride is found and the authors suggest that this indicates developing permeability to sodium. Since electrical activity is also noted at about this time, it seems possible to the reviewer that the excess sodium in the nerve cells may represent, not a change in permeability, but a new steady state level due to intermittent action of an outward sodium transport mechanism; whereas, prior to nervous activity, uninterrupted outward transport was the rule.

Lansing *et al.* (50) demonstrate a rapid exchange of Ca^{45} in the soft tissues of mice. This is regarded as an ion exchange phenomenon, and certain hyperplastic and carcinomous conditions of the epidermis lead to decreased exchange.

Single cells.—A number of studies have been made of the permeability of the erythrocyte to inorganic elements commonly present. In this connection, special attention is called to the important series of papers by Ponder (51 to 56). Space does not permit detailed discussion. Ponder has been

concerned primarily with tonicity volume relationships of erythrocytes and offers extensive data on loss of potassium under a variety of conditions.

Greig & Holland (57, 58) have noted effects of acetylcholine and anticholinesterases on permeability of erythrocytes to potassium. For frog erythrocytes, Harris & Burn (17) report a permeability of 9×10^{-5} cm. per hr. for potassium or 2×10^{-6} cm. per hr. for sodium. Other papers dealing with erythrocytes will be mentioned later (Table I).

TABLE I
CELL, TISSUE, OR ORGANISM PERMEABILITY

Object	Substance or Phenomenon	Comments	Authors
Yeast	cobalt	600X accumulation effect of nickel	Nickerson & Zehahn (143)
Yeast	phosphate	600X accumulation effect of nickel	Batta & LeCoq (144)
Erythrocytes	anions	narcotic effects	Liebe (145)
Erythrocytes	hemolysis	organic calcium effects	Hahn & Bruns (146)
Erythrocytes	hemolysis	histamine effects	Zacco & DeVita (147)
Erythrocytes	hemolysis	Q ₁₀	Luckner (148)
Erythrocytes	hemolysis	glycolytic poisons	Rummel (149)
Sea urchin egg	osmotic behavior	ultraviolet effects	Reed (150)
Insect egg	iodine	development	Slifer (151)
Insect egg	water loss	development and temperature	Beament (152, 153)
Insect larvae	trivalent arsenic	development	Ricks & Hoskins (154)
Insect larvae	potassium chloride, urea, etc.	electrical and chemical studies	Richards & Fan (155)
Tetrahymena	succinate	increase with cyclopentane derivatives	Seaman & Houlihan (156)
Muscles	osmotic behavior	effects of adrenalectomy	Angerer & Angerer (157)
Bacteria	proflavin	concentration effects	Jackson & Hinshelwood (158)
Synovial membrane	phenol sulfonaphthalein	effects of hyaluronidase and steroids	Seifter <i>et al.</i> (159)
Various tissues	osmotic behavior	effects of hyaluronidase and steroids	Seifter <i>et al.</i> (160)
Capillary	protein	oxygen effects	Henry <i>et al.</i> (161)
Skin and Chara	salicylates	cation effects	Halpern <i>et al.</i> (162, 163)
Tooth enamel	methylene blue	morphological and electrical studies	Atkinson (164)

Wilson & Manery (59) have published an interesting study showing the permeability of rabbit leucocytes to sodium, potassium, and chloride. Permeability to all three elements could be demonstrated by following concentration changes within the cells, with a rapid, nearly complete exchange of Na²⁴. A noteworthy study by Abelson & Duryee (60), which will be mentioned in more detail later, shows the rapid entrance of Na²⁴ into frog ovarian eggs.

Cowie *et al.* (61), using Na²⁴ and K⁴⁰, conclude that *Escherichia coli* is freely permeable to both elements. Studies on the exchange of potassium

ion and hydrogen ion by yeast have been continued by Conway (62, 63). Ørskov (64) concludes that potassium uptake by yeast is to be related to a primary energy source in the environment rather than to any specific nutrient or to the formation of any special product of assimilation. Schmidt *et al.* (65) record the interesting observation that, while yeast is assimilating phosphate from a normal medium, potassium is taken up; but, in the absence of magnesium ion, sodium is taken into the cells in excess.

A very extensive and valuable summary is given by Malm (66) of her studies on permeability of yeast to sugars, fluoride, and other substances.

ACCUMULATION AND ACTIVE TRANSPORT OF IONS

The reviews of Ussing (9), Krogh (67) and Rosenberg (68) should be referred to for basic discussions. Since all available evidence indicates a permeability of muscle, nerve, and some other cell types to the major inorganic elements of the environment, with at least a small part of the penetration in a form leading to real internal concentration changes (i.e., free diffusion, ion transport other than simple exchange phenomena) it is imperative to consider, first, the evidence for the need of active ion transport and second, possible mechanisms.

Conway [cf. (69)] has developed, with great care, a concept involving the exclusion of sodium and the passive distribution of potassium and chloride in muscle fibers, showing that high internal potassium is a necessary consequence of sodium exclusion. Ussing (5, 9) also gives calculations which indicate a passive distribution of potassium. Granting these considerations, it follows that sodium must be excluded by an impermeability of the membrane or by active outward transport or, most probably, by a combination of the two.

If a true impermeability is the basis for the ion distribution, then it follows that if a cell once admits, for example, sodium to which it is normally impermeable, there can never be any recovery of the original condition. On the other hand, if the apparent impermeability (see Teorell's comments on "false impermeability") is achieved by active outward transport of sodium, recovery would be possible and, indeed, necessary.

Unfortunately, most studies showing loss of potassium from cells and gain of sodium have not been extended to the reverse processes. The outward movement of potassium and inward movement of sodium upon, for example, stimulation, could be simply a passive diffusion due to chemical gradients in a system whose vital activity was momentarily decreased. The reverse process, however, demands a selective and active transport system, presumably for sodium (16).

Conway & Hingerty (70) report on recovery of rats whose muscles were made low-potassium and high-sodium by feeding a potassium deficient diet. Upon return to a normal diet, potassium levels were rapidly restored; sodium levels returned to normal only after several days. The authors conclude that there is a very slow outward transport of sodium with the muscle

fiber normally virtually impermeable to sodium ions. This result raises interesting questions, since earlier work by Fenn & Cobb (71) on similar animals showed a nearly comparable loss of potassium and gain of sodium during an hour or so period of stimulation, with a half time of recovery during rest of only 1 to 3 hr. for both sodium and potassium. It is possible, though not indicated by experimental data, that sodium and potassium shifts during dietary alterations are different from those during stimulation and recovery or perhaps the potassium deficient diet was deficient in other unknown factors concerned with sodium transport. The pathological changes noted in excessively high-sodium, low-potassium diets may be relevant (72).

The striking case of reversible exchange of sodium and potassium has been further examined by Flynn & Maizels (73) in human erythrocytes. Low temperature storage results in loss of potassium and gain of sodium. The changes are reversed upon incubating the cells at a higher temperature in the presence of glucose. The authors speculate briefly on the relationships of human erythrocytes to those of other species of mammals normally containing high sodium, pointing out that either an increase of permeability or a decrease of outward transport of sodium could account for the difference. While Flynn & Maizels (73) conclude that an outward transport of sodium ion is the major active process, Ponder (74), considering new as well as old evidence, suggests an active accumulation of potassium may also be operative.

Studies on acid secretion, while pertinent to the present discussion, are reported in other reviews dealing with the digestive system. Special reference should be made to the studies of electrical and metabolic factors by Davies & Ogston (75), secretion and pressure by Davies & Turner (76) and papers of more general scope on mechanisms of acid formation by Conway (62, 63).

BOUND AND NONEXCHANGEABLE INORGANIC ELEMENTS

Suggestions that ion accumulation may relate to specific binding by cell constituents are made frequently and isotope studies in some instances show incomplete exchange. Stone & Shapiro (77) ultrafiltered muscle brei and claimed to have demonstrated a potassium binding by the non-filterable components with complete diffusibility of sodium. Unfortunately, the published figures referred only to analyses of filtrates, hence it is impossible to assess the possibility that contamination, especially with sodium, was not operative. Carr & Topol (78), using membranes as reversible electrodes, determined sodium and chloride activity in solutions with and without protein present. At acid pH values, neither gelatin nor casein influenced inorganic ion activity. At alkaline pH values, however, measurements indicated up to 25 per cent sodium binding. It seems possible to the reviewer that an increase in ionization of phosphate groups of casein might account for the apparent binding.

The study by Abelson & Duryee (60) showed only a 12 per cent initial

exchange of sodium in frogs eggs, followed by a very slow continued uptake of isotope. Washing out experiments showed essentially similar results, initial movements of sodium in either direction being rapid. Radio-autographs failed to show any morphological compartmentalization to account for the two sodium fractions, although the nucleus exchanged proportionally more Na^{24} than the cytoplasm. Rothenberg (18) found about a 10 per cent exchange of potassium in squid nerve and a complete equilibrium of sodium, and Harris & Burn (17) report complete exchange of both sodium and potassium in frog muscle.

Thus, in different cell types, sodium and potassium are reported as either completely or incompletely exchangeable. To the reviewer's knowledge there is no good suggestion to account for these compartmentalizations, since, in view of the high electrical conductivity of protoplasm, simple ion binding (i.e., marked decrease in activity) would not appear to be plausible. Striated muscle fibers have a visible morphological compartmentalization (79) but they show complete exchange of potassium. Squid nerve axoplasm shows little morphological differentiation that could be invoked, especially since neurotubules appear not to exist as normal components of axoplasm (80). Roberts *et al.* (81) suggest that the high potassium content of *E. coli* relates to a binding by hexose phosphates, but the reviewer knows of no justification in the chemistry of these compounds to indicate such a binding. Since death of muscle or nerve fibers leads to a rapid equilibration with the inorganic elements of the environment, some very dynamic but exclusive system would seem indicated to account for compartmentalization of the materials in question.

It is regrettable that more precise information about ion binding, particularly of the alkali metals, is not available. While it seems unlikely that the large concentration differences noted for intracellular and extracellular potassium can be related to simple ion binding, from the physiological evidence available, specific binding of ions such as sodium as contrasted to potassium is strongly indicated. In one instance, at least, in inorganic chemistry, a compound which may be analogous to biologically important compounds binds sodium firmly but not potassium (82). It seems probable that selective binding (8) of ions at various interfaces, cell surfaces, and intracellular surfaces will be found to be increasingly important in future work. Hutner (83, 84) has discussed possible roles of "chelating" agents in this respect. Special attention should also be drawn to the solubilizing action of various phosphate compounds as studied recently by Neuberger & Mandl (85) and Neuberger & Roberts (86). Eddy & Hinshelwood (87) discuss potassium uptake by *Bacterium lactis aerogenes* in terms of specific binding at active centers necessary for growth.

PERMEABILITY TO ORGANIC SUBSTANCES

There have been relatively few studies, in the classical tradition, of comparing permeability of cells to members of a series of organic compounds.

Green (88) has made a precise spectroscopic study of the penetration of fatty acids into erythrocytes. Flexner *et al.* (89) studied the permeability of guinea pig capillaries to radioactive ferric β -globulin, finding its passage about 100 times slower than water. Uptakes of dyes (90) and enzymes (91) by yeast have been studied. The passage of various penicillin preparations through the placenta is reported (92) and also the kinetics of penetration of anti-helminthics into *Ascaris* (93). The abilities of various Nematode worms to take up P^{32} from host tissues are compared (94).

Jacobs *et al.* (95) have summarized their studies on hemolysis of erythrocytes of various vertebrates. Instructive diagrams illustrating relationships with respect to penetration of several organic solutes are presented. A critical discussion of the detection of osmotic abnormalities of erythrocytes is also given (96).

Electron microscope studies by Lindeman (97) of erythrocyte ghosts after osmotic hemolysis show that membranes remain intact during loss of hemoglobin. Jung (98) has reviewed recent work on the structure of the erythrocyte with special reference to the state of hemoglobin.

ACCUMULATION AND TRANSPORT OF ORGANIC SUBSTANCES

In an important paper, Stern *et al.* (4) report on the uptake and accumulation of glutamate by brain slices. An inward transport occurs against a gradient. Glucose is the best substrate for supporting the transport but some others will suffice. The paper should be consulted for details. Using kidney slices, Cross & Taggart (99) have studied uptake of *p*-aminohippurate in similar fashion. LeFevre (100) reports that copper and various sulfhydryl agents depress permeability of erythrocytes to glycerol and sugar, the effects of some of the agents being reversed by glutathione and cysteine. He suggests surface phosphorylation as a first step in the passage of sugar, glycerol, and like substances across the membrane. Jacobs (101) discusses these and similar results in a recent review.

Accumulation and transport of organic materials, as related to kidney function and intestinal absorption are treated elsewhere (102, 103).

PERMEABILITY TO WATER AND OSMOTIC BEHAVIOR

A recent series of discussions includes consideration, among other things, of water movements in plants (104, 105) and through insect cuticle (106, 107). While the experimental observations are most interesting, theories regarding mechanisms involved in what is apparently a true active transport of water are neither complete nor simple of comprehension. The discussions cited should be read by all interested in the subject of water movement and permeability.

Water relations of plant cells are also considered by Thoday (108) and Arens comments briefly on active water transport, invoking electrical forces (109). Seeman (110) finds, using plasmolysis methods, a decrease in permeability to water of plant cells in low or high pH, with a plateau region of nor-

mal permeability around neutrality. The interesting movements of water in *Nitella* cells, discussed in the last review, have been further investigated by Osterhout (111, 112). Regional internal differences of osmotic pressure are related to water movements through the cells. The same author (113) reports on abnormal protoplasmic patterns in *Nitella* upon slight plasmolysis. Also, passage of electric currents through *Nereis* eggs causes marked water uptake, apparently due to swelling of cortical granules (114).

Opie (115) attempts to define various isotonic solutions by noting volume changes in tissue chunks. Using the term "isotonic" in its classical sense (= solution in which cells do not change volume) great diversity is shown for different tissues in different salt solutions. In this connection, the reviewer wishes to note that there is considerable difference in usage of the word "isotonic," most medical texts adopting the definition noted above and many research papers using it to designate solutions of freezing point depression equal to that of the normal environment of animal cells. Ponder (53) uses "isoplethochontic" to characterize solutions in which cell volume is maintained, a word which sacrifices euphoniousness to accuracy.

Shapiro (116) finds the nonsolvent space (b value) for *Arbacia* and *Chaetopterus* eggs to change upon fertilization, the decrease and increase respectively roughly paralleling changes in Q_{O_2} . Further studies attempting to define the physiological significance of this "constant" would be desirable.

In a review on the biology of viruses, Anderson (117) notes the apparent osmotic behavior of certain of the bacteriophages (T_2 , T_4 , T_6) which seem to possess membranes. Rapid shifts from high to low salt environments cause inactivation, slow changes do not. The inference can be made that the viruses are permeable to water and slowly permeable to salts. Wilbrandt (118) has investigated further "colloid osmotic hemolysis," a term he introduced to describe the osmotic hemolysis due to increased cation permeability of erythrocytes.

PHOSPHATE UPTAKE BY CELLS

This subject, while treated in other reviews [e.g. (119, 120, 126)], is mentioned briefly here because of the possible use of mechanisms of phosphate uptake as model systems for assimilation of other, especially inorganic, components of the environment. Previous reference has been made to the work of Spiegelman & Kamen (7) indicating that uptake of phosphorus by yeast involves combination with organic material at or near the surface of the cell. Kamen & Spiegelman (120) should also be consulted. Interesting papers by Rothstein and co-workers (121, 122) supply information which should be of great value in elucidating mechanisms of active uptake of material by living cells. Among other things, it seems to the reviewer that the surface localizations of esterases, aside from possible participation in synthesis, may act as safety controls to prevent undue amounts of metabolic intermediates from entering the cell from the outside. Yeast can utilize hexose phosphate of the environment when surface enzymes are intact, phosphate

appearing in the medium. Poisoning of the surface enzymes stops utilization of sugar phosphates, although sugar can still be metabolized (123).

Phosphate and glucose assimilation appear to be interdependent in yeast (124). Schmidt *et al.* (65) note that normal assimilation of phosphate requires potassium in the medium. The rate of uptake of P^{32} and rate of growth of *E. coli* are parallel, most of the intracellular P^{32} being nondialyzable (125).

Sacks (126) has reviewed his work indicating that the uptake of phosphate by muscle fibers is an active process involving formation of organic phosphate at the cell surface. An interesting report by Goffin *et al.* (127) gives the results of seeding a lake with P^{32} . Plankton took up the element rapidly, fish after about 50 hr., and marginal trees after about two weeks. Villee *et al.* (128) have reported on the uptake of P^{32} by sea urchin eggs and its intracellular distribution.

MODEL SYSTEMS AND THEORY

An informative and interesting discussion of the diffusion of ions across phase boundaries is given by Davies (129). The role of diffusion of solvate molecules away from solute when the latter enters a new phase is especially emphasized. Due to these complications, diffusion through the surface may be very slow as compared to diffusion in the bulk of any one phase. Activation energies for diffusion of potassium salts through cupric ferrocyanide membranes are reported by Tolliday *et al.* (32) to be in the neighborhood of 5,000 cal. per mol. as compared to around 4,000 for free diffusion in water. Space does not permit extensive review of the papers by Sollner & Gregor (130, 131) on "permeable" membranes and by Sollner (132, 133) on "bi-ionic potentials." Weatherby (134) has studied an artificial phospholipid membrane. Lipid and lipoprotein contributions to membrane properties of cells have been discussed by Chargaff (135), Ponder (136), and Booiij (137).

Barrer & Jost (138) comment on interstitial diffusion, noting that diffusion coefficients in zeolite-like systems may decrease as the interstitial concentration of sorbate increases. The role of diffusion in the combination of chlorine with wool has been treated by Alexander *et al.* (139). Hartley & Crank (140) discuss fundamental concepts and definitions of diffusion. Hearon (141) treats mathematically cases of simultaneous diffusion streams, showing the degrees of interactions to be expected [cf. (2)].

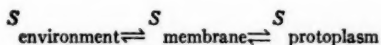
Using hemoglobin as an indicator, Müller (142) has studied the diffusion of oxygen through water and hemoglobin solution layers. The movement of gas through water layers follows Fick's law well, although the diffusion constant varied with hemoglobin concentration. Diffusion rates through hemoglobin layers were lower than through water, for stationary gradients the ratio of rate through water to rate through 16 per cent hemoglobin being 1.5.

COMMENTS

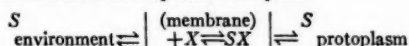
It is the opinion of the reviewer that concepts of permeability have been clouded by oversimplification. Given a substance *S*, placed in the environ-

ment of the cell, then that substance could enter the aqueous interior protoplasm by several mechanisms.

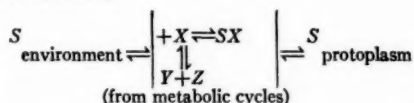
1. The substance could penetrate through holes or by solution in the membrane.



2. The substance could form a specific complex.



3. The complex could be energetically formed and/or broken down (i.e., coupled to oxidative systems).



In case 1, the conditions are the simplest and movement of S should proceed to an equilibrium and at a rate defined by the usual rules of diffusion. In case 2, a possible high degree of specificity is added plus the restriction that complex formation might limit the rate of movement of S , rather than concentration (=electrochemical) gradients. In case 3, there is a possibility of active selective transport. The conditions of case 1 are assumed to hold by many workers, usually not explicitly. Formation of un-ionized complexes (case 2) has long been advocated by Osterhout to account for selective ion uptake by *Nitella* and *Valonia*. The conditions for case 3 have perhaps been most explicitly stated for the instance of resorption of sugar by the kidney tubules.

A cell could presumably be completely impermeable to a substance as defined in case 1, while showing rapid exchange and/or transport according to cases 2 and 3. From the literature cited, it is obvious that there is a distinct tendency for recent observations to be interpreted in terms of 2 and 3 rather than 1. In other words, much evidence is consistent with the view that many substances penetrate by first being incorporated into the substance of the cell (assimilation). Whatever the merits of this point of view, it is more satisfying to the physiologist, since a substance entering the cell through a hole seems quite uninspiring as compared to a substance combined with other protoplasmic constituents.

It is, of course, necessary to point out that terms such as "uptake," "complex formation" and "active transport" can be very dangerous if bandied around loosely. A primary requirement, before invoking the terms, should be that of showing that the "simple diffusion" of case 1 does not work.

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THE BIOLOGICAL EFFECTS OF RADIATIONS

BY HOWARD J. CURTIS

*Department of Physiology, Vanderbilt University, School of Medicine,
Nashville, Tennessee*

THE BIOLOGICAL EFFECTS OF RADIATIONS

The study of the biological effects of ionizing radiations has increased enormously in the past few years, largely because of the development of atomic energy, with its attendant hazards and potentialities. This interest is reflected in the large number of papers published in this general field during the past year. For this reason it has been necessary to limit the coverage of this review, and thus exclude many papers normally considered in this field.

The papers covered deal rather strictly with the field of Radiobiology, defined as being a study of the effects of ionizing radiations on living systems. This excludes the many papers on the toxicity of compounds normally associated with this field; health physics and papers having to do with instrumentation in this field; all papers dealing with roentgenology and x-ray and radium therapy; those dealing with the therapeutic uses of radioactive isotopes; those pertaining to the use of radioactive tracers; and all papers dealing with the use of radiation as a tool in some biological study such as studies in genetics.

There have been a number of papers of general interest in the field. Warren has published two papers (1, 2) on the clinical problems associated with atomic energy. He gives a detailed account of the acute radiation syndrome, especially its pathological aspects, and stresses the point that there is no specific agent which has been found to be particularly beneficial in this case, but general supportive measures are recommended. Jacobson, Stone & Allen (3) also discuss the problems facing the physician in cases of over-exposures to penetrating radiations such as might be encountered in atomic warfare. They discuss the role of transfusions, antibiotics, and antiheparins in the treatment of such cases. Behrens (4) has published a book *Atomic Medicine* in which the entire field is covered. However, this book belongs in the popular rather than the scientific or medical literature.

Ellis (5) discusses the general problem of personnel protection from radiation and stresses particularly the fact that there is no such thing as a "tolerance" dose of radiation. He feels that the greatest single hazard is the development of leukemia, and thinks that if the blood count of workers in this field is followed carefully it will give an adequate indication of over-exposure. However, Glücksman (6) discusses this problem from a more fundamental point of view. He points out that until more fundamental information is available we can do no more than hazard guesses at the maximum permissible doses of radiation. This is in agreement with the work of Knowlton (7) who

concludes that an exposure of 0.2 r per week cannot be detected in individual cases even when the blood counts are followed carefully, yet feels that some damage may be taking place even at this dosage rate. However, he feels that blood counts represent the best available index of acute radiation damage.

It should be mentioned that Marinelli (8) has computed the tissue dose of radiation in connection with the concentration of various common radioactive isotopes in tissues for a wide variety of different situations.

Ingram (9) has discussed the safeguards which must be taken when working in the laboratory with radioactive materials and the consequences of ignoring them, while Molloy & Beckman (10) describe the various types of instruments available for radiation detection. Marley (11) describes the types of barriers which must be used in connection with work with very high energy radiations.

Williams (12) found that at the Atomic Energy Research Establishment at Harwell, England, it is possible to keep exposure below 0.1 r per week, which is in accord with experience in the United States. Indeed Spalding, De Amicis & Cowing (13) found, on analyzing film badges, that the average x-ray worker receives far more radiation than the worker in the field of atomic energy.

A number of papers describe the effects of exposure to an atomic bomb. Novy (14) describes the condition of the skin of the survivors at Hiroshima three years after the blast, and could find no instance of clear cut injury attributable to the radiations. A similar study was made of the blood two years after the blast by Snell, Neel & Ishibashi (15). They found only very minor abnormalities. Bernier (16) has just published the results of his studies of the lesions in the mouths of persons severely exposed at Hiroshima and Nagasaki. He found the epithelium of the mouth to be quite sensitive to radiation, probably reflecting the damage to the rest of the gastro-intestinal tract. The Atomic Bomb Investigating Group has made a report (17) describing the pathology of the acute skin lesions of some of the victims.

Tullis (18) has made an extensive morphological study of the tissues of pigs exposed at Bikini. The changes found agree perfectly with predictions from earlier work. This is also true of the similar studies of Lawrason & Cronkite (19) who studied blood changes in these same pigs.

There has been considerable difference of opinion as to the maximum amount of radiation which should be allowed any person because of damage to the germinal cells. Evans (135) assumed that the spontaneous mutation rate in the human is the same as in *Drosophila*, i.e., about 10^{-8} per gene. Further, he takes the radiation-induced mutation rate as 3×10^{-8} per gene per roentgen (r). From this it is seen that if everyone in a population were to receive a dose of 300 r, the mutation rate in that population would be doubled. However, these radiation-induced mutations are almost certainly recessive, and therefore the effect of a single dose to one entire generation would tend to die out after several generations. Further, Evans computes that if 5 per cent of the present generation of man were to receive a dose of

300 r before the child-bearing age, then the mutation rate among humans would be only 8 per cent above the spontaneous mutation rate after 2,000 years. He does not consider this serious, since he assumes the spontaneous rate in humans to be very small. His final conclusion is that "no detectable increase in hereditary abnormalities is likely to result, even after many generations, if a small fraction of the population receives daily radiation doses up to 0.1 r per day."

Müller (136) does not agree with this. He argues that if you agree to allow a daily exposure up to 0.1 r per day, then because of x-ray examinations, etc., we must expect that the entire population, male and female, will receive about 100 r before the child-bearing age. After some generations this will cause a doubling of the spontaneous mutation rate. He further assumes that 99 per cent of all mutations are bad, that in our present society such deleterious mutants are not eliminated by natural selection, and that the present spontaneous mutation rate in the human race is quite high. He feels that many of the characteristics which differentiate healthy people from people predisposed to disease, for example, are the result of recessive mutations. If such abnormalities were to be doubled in the population, a great many people would find life a burden. He is also worried about the number of lethal mutations, which would presumably cause a slight decrease in fertility after many generations.

These considerations are of tremendous practical importance, since the maximum allowable radiation exposure is based on the answer to this genetic problem. It should be emphasized that both of these calculations are based on guesses, since the necessary data is lacking and will be for several hundred years. It is probably safe to say that most investigators would tend to agree with Evans, but vote with Müller. Consequently, the maximum allowable exposure to radiation at Atomic Energy Commission installations has been reduced from 0.1 r per day to 0.3 r per week.

There continues to be a good deal of interest in the comparison of the biological effects of different radiations. In a report by Curtis & Teresi, which has been declassified (137), the effects of slow neutrons on tissues are treated in some detail, both theoretically and experimentally. The amount and kind of radioactive materials induced in tissues as a result of slow neutron bombardment is found to be exactly what one would expect on theoretical grounds. Phosphorus and sodium are the most dangerous elements in this regard. However, it is shown that in a human this radiation will produce only about 1 per cent of the biological effect produced by a slow neutron exposure, the rest being due to radiations emitted at the time of the exposure. An overexposure to slow neutrons could be estimated from a urinalysis for either radioactive sodium or phosphorus. A maximum allowable dose of slow neutrons has been computed as an 8 hour exposure in flux of 9×10^8 neutrons per sq. cm. per sec.

Tait (20) has re-calculated the maximum permissible tolerance dose for slow neutrons, and Biram (21) and Tait (22) have calculated the penetration

and effects of fast neutrons in soft tissues. Skaggs (23) finds 20 million electron volt (M.e.v.) x-rays about 70 per cent as effective as 200 electron kilovolt (e.kv.) x-rays in producing mutations in *Drosophila*. Quastler (24) found that in mice the two radiations were equally effective in producing acute death, but the high energy radiation was somewhat less effective in producing delayed effects. Zirkle (25) discusses the phenomenon of additivity of α -rays, β -rays, γ -rays, and fast neutrons. He concludes that the available data indicates that these radiations are additive in most of their biological effects, and therefore the fundamental mechanism of action must be similar. This is not in accord with the preliminary report of Bateman & Sinclair (26), who found that when the lethal mutations of *Drosophila* were studied, x-rays and β -rays were about equally effective, but for visible mutations the β -rays, from injected P^{32} were four times more effective. Snyder & Kisieleski (27) compare the effectiveness of β - and x-rays in mice by giving doses of Na^{24} , and find x-rays more effective by a factor of 1.4. It is extremely difficult in these comparative studies to make sure that the tissue doses are the same in the two cases.

Conger & Giles (28) found that slow neutrons are about 11 times more efficient than x-rays in producing chromosome aberrations in *Tradescantia*, when compared on an equal ionization basis. This is due not only to the greater biological effectiveness of the secondary particles resulting from slow neutron capture, but also due to the fact that they originate in a very sensitive part of the cell. The same conclusions were reached by Frolik & Morris (29), who exposed Maize pollen to slow neutrons and found a large number of mutations.

Skaggs (30) has worked out the depth dose for radiation from a 20 M.e.v. betatron by phantom measurements and finds, in accord with Quastler's (31) calculations, that the deep tissue dose is larger than the skin dose.

There continue to be reports of the stimulating effect of radiations. Hoffman & Wollman (32) report an increase in the rate of migration of cells from adult chicken cardiac muscle as a result of small doses of x-rays (30 r) while larger doses (1,000 r) inhibit migration. In the other hand Pohle, Ritchie & Moir (33) tried to find a stimulating effect of low doses of x-rays on wound healing and failed.

The recent trend in the theoretical interpretation of x-ray data seems to be away from the "target theory" as it was originally proposed. Minder (34) discusses this and concludes that the "target volume" bears no relation to morphological structures within the cell. Sanden (35) has attempted to modify the theory to account for the observed dose-effect curve in terms of the ionization density. Gray (36) feels that none of the current theories is adequate to explain even a large fraction of the observed effects. Zirkle (37) is tending to think more and more of biological effects in terms of activated chemical reactions. Farmer, Stein & Weiss (38) discuss the possible chemical reactions.

This does not mean that the target theory does not involve useful con-

cepts. For example, Latarjet & Ephrussi (39) published an important paper showing that the killing curves for a haploid yeast follow a one-hit curve and that diploid cells from the same strain follow a two-hit curve. Giles & Conger find chromosomal interchanges in *Tradescantia* to be a one-hit phenomenon, and conclude that several ionizations must take place in a nucleus to cause a break.

As contrasted with these views, Schubert (40) explains all effects in terms of the target theory, and Opatowski (41) has even used the target theory to compute the sensitive volume in the tobacco mosaic virus and finds it to be the same as a nucleic acid molecule. On the basis of the ionization density, he then concludes that only a quarter of the nucleic acid molecules are involved in chromosome breaks.

There is an increasing body of knowledge indicating that many of the observed biological effects are due to the inactivation of enzymes. Feinstein, Butler & Hendley (42) found the same inactivation of liver catalase in mice by injection of hydrogen peroxide as by x-rays *in vivo*, and concluded that the mechanism of action of x-rays is by peroxide formation, which in turn inactivates enzymes. Bacq, Lecomte & Herve (43) reach the same conclusion after a study of the effects of x-rays and β -rays on excised frog muscle. Tahmisian (44) studied the changes in the enzyme systems in grasshopper eggs following large doses of x-rays, and concluded that anabolic enzyme systems are more sensitive to radiation than are catabolic systems.

Barron and his group (45) have continued to pile up evidence pointing to the fact that the enzymes containing sulfhydryl groups are the ones most sensitive to x-rays. He found that in dilute suspensions of sea urchin sperm the inhibition of respiration by x-rays was increased in the presence of succinate or acetate substrates. Furthermore, he concluded that there is far too much catalase present in sperm to allow the respiration to be decreased by peroxide formation, so the x-ray inhibition in this case must be by some other mechanism.

Kirschner, Prosser & Quastler (46) find that in rats there is an increase in oxygen consumption following irradiation by as much as 58 per cent. This would seem to indicate that x-rays acted to speed up metabolism in the mammal. However, the increased oxygen consumption did not correspond to the weight loss, indicating that other factors must be present. Dowdy, Bennett & Chastain (47) exposed rats in very low oxygen tensions (5 per cent) and found that the acute effects of radiation are only half as severe. This supports the theory that irradiation injury results from radio-chemical reactions involving free oxygen. Haley, Mann & Dowdy (48) tested the ability of normal and hypothyroid mice to withstand x-irradiation. They found that the hypothyroid state does not protect the mice and conclude that it is the oxygen tension in the tissues which determines the sensitivity and not the rate of oxygen utilization. This is confirmed by Smith *et al.* (49) who found that mice die only slightly more readily following x-rays if they are kept cold enough to increase their metabolism considerably. This picture is complicated by the

experiments of Patt, Swift & Tyree (50) who found that the metabolism of irradiated frogs is not increased.

Baker & Sgourakis (51) subjected male *Drosophila* to x-irradiation at low oxygen tensions and different temperatures. They found an increased number of mutations in the flies exposed at low temperature, and attribute this to the fact that there was more dissolved oxygen at the lower temperatures. This is confirmed by Giles & Riley (52) for *Tradescantia*, who found chromosome aberrations greatly diminished when the plants were irradiated in an atmosphere of other gases such as argon, helium, or nitrogen, which excluded oxygen. Further, aberrations were greatly increased in an atmosphere of pure oxygen. Results obtained with tadpoles complicate the picture since Allen, Schjelde & Hochwald (53) found that the temperature at which they are irradiated makes no difference in the amount of cellular damage produced.

Rollason (54) studied the development of frog's eggs following x-ray treatments at different times after fertilization, and found that the time of treatment was not important in determining the ultimate development. This is in accord with the work of Brunst & Brunst (55) who fractionated the dose of x-rays to amphibia, kept at rather low temperatures, and found that the doses add quite accurately, which could be interpreted to mean that at low temperatures there is no recovery, although it takes relatively longer for the effects to become manifest. Almost identical results were also found by Lamarque & Gros (56).

It is becoming apparent that the same type of effects occur in plants following irradiation as in animals. Quastler & Baer (57) have given an excellent account of the effects of irradiating bean seedlings at different stages of growth, and describe a number of different abnormalities. Granhall *et al.* (58) describe the effects of irradiating scions of fruit trees with moderate doses of x-ray. Somatic mutations occur, giving trees which have somewhat different fruit and show different resistance to disease. The authors are quite enthusiastic about this as a method of producing new and better fruit trees. Russell, Adams & Martin (59) show that root growth is very sensitive to radiation, and plants grown in water culture with a P^{32} concentration of only 10 microcuries per liter will be stunted. As in animals, it takes enormous doses of radiation to produce immediate effects. Bishop, McLaughlin & Topley (60) found that it took about 700,000 r to stop protoplasmic streaming in *Tradescantia*. Also, the search for a stimulating action of radiation seems no more successful. A group at the U. S. Department of Agriculture (61) failed to confirm, on a rigid scientific basis, previous reports that certain radioactive materials spread on a field as a fertilizer will increase crop yield. Also Suskind (62) failed to confirm an earlier report that seeds which have been inactivated by heat can be resuscitated by x-rays.

Buchsbaum & Zirkle (63) have succeeded in irradiating only certain parts of amphibian erythrocytes with alpha particles. They find that there is an initial shrinkage of the irradiated part of the cell, followed by swelling and a rupture of the cell. This clearly demonstrates an extra-nuclear effect of

the radiation. Duryee (64), in an extended study of the x-ray effects in single cells, is able to withdraw some of the cytoplasm from an irradiated cell and inject it into a normal cell. Under these conditions, the injected cell exhibits typical radiation effects. He concludes from this and a good deal of other evidence that "cellular radiation damage is a triple phenomenon, consisting of: primary physical or radiochemical changes in cytoplasm; chemical metabolic processes which allow protoplasmic nuclear toxins to form or accumulate in the cytoplasm; and, transmission of toxic substances into the nucleus in 10 to 30 min. at 23°C." Kimball (65), using paramecia, has studied protoplasmic inheritance and tentatively suggests that it may follow a "one-hit" curve.

Rugh (66) describes in detail the chromosomal changes induced in salamander cells as a result of x-irradiation. Carlson (67) describes the effects of both ultraviolet and x-ray on mitosis in grasshopper embryo neuroblasts. He finds there is no "critical period" during mitosis for blocking mitosis, but the cell is most sensitive during late prophase.

Brunst (68) studied the effects of x-rays on regenerating limb buds, in amphibia, and finds that even though the cells seem to regain their original histological appearance, they either fail to grow or are considerably retarded. This was confirmed in another way by Dent (69) who, injected P₃₂ intra-peritoneally before excising the limb. These somatic mutations have been studied extensively by Chase (70) for the case of the graying of hair in mice. By plucking the hair and allowing it to re-grow, the state of activity of the follicular cells was changed. He found them to be most sensitive to somatic mutations when resting.

Patt and his group have written a very significant series of papers (71 to 74) on the effect of the injection of cysteine on the x-ray mortality of rats. They find that cysteine, but not cystine, injected before, but not after, x-irradiation has a very significant effect on survival. The LD-50 dose is nearly doubled in some cases. The mechanism of action is not known, but it is possible to make some intelligent guesses. A number of authors have emphasized the action of radiation on water to form peroxide or other decomposition products which are strong oxidizing agents. Barron especially has pointed out that the sulfhydryl-containing enzymes are readily oxidized by x-rays and may be protected from them, *in vitro*, by a reducing agent such as glutathione. On this basis, then, one would assume that the cysteine was acting as a reducing agent in the tissues, if not intracellularly.

This hypothesis gains support in the work of Baq and his group (75, 76, 77) who found that sodium cyanide, if injected intravenously in just sublethal doses to mice before x-irradiation, will significantly reduce mortality. They give two possible explanations of this action, first, that the cyanide inhibits the formation of peroxide by the x-rays, and second, that the cyanide ion forms a loose bond with sulfhydryl radicals to prevent their oxidation by the peroxide formed by x-rays. The former of these views seems to be strengthened by his finding that α -tocopherol also protects mice a little, and it is known that this substance is very effective in inhibiting peroxide forma-

tion *in vitro*. It is significant that sodium sulfocyanate is ineffective in this connection. It may be recalled that the oxygen concentration is an important variable in x-ray studies (51, 52).

Nizet, Heusghem & Herve (78) draw a parallel between x-ray treatment and other forms of stress. They treated the hind limbs of rabbits with large doses of x-rays and assayed the adrenal glands at varying times after treatment for 17-ketosteroids. They found that the loss occurred more rapidly than in other forms of stress, but persisted for a shorter time. This would indicate that radiation is a stress in this sense only during the actual time of treatment. This is not in accord with the work of Lawrence (79) who measured the urinary output of 17-ketosteroids in dogs following minimal lethal doses of total body x-irradiation. He demonstrated that the excretion increased to a peak at about the 9th post-irradiation day and slowly returned to normal. This is much more in keeping with what one would expect on the basis of other known physiological changes. It is significant in this connection that Edelman (138) has found that if the adrenal glands only are shielded then the mortality in rats subjected to total body x-irradiation is very significantly decreased.

There have been many attempts to alter the course of the radiation syndrome in the mammal by various drugs. Selle (80) has written a very concise review of the work in this field through 1948. Fetzner & Werle (81) find that the acute radiation sickness as seen clinically is due to the release of histamine and treat it successfully with antihistamines. Likewise, Setälä & Ermala (82) studied the change in chylomicron count following x-irradiation in patients and find it is directly proportional to the severity of the sickness. Histamine produces the same type of chylomicron response. Haley & Harris (83) tried to alter the course of the radiation syndrome in guinea pigs with antihistamines, and failed. This does not necessarily contradict the above findings, since they were undoubtedly measuring quite different effects. Salva & Badell (84) tried a number of different antihistamines for the treatment of clinical radiation sickness and found phenergan to be the best. Beeler, Tillisch & Popp (85) recommend dramamine for radiation sickness, while Larkin (86) feels that atropine may be helpful in certain cases. There would seem to be at least some rationale for atropine from the work of Vieten (87) who concludes that acute radiation sickness is due to a direct action of the radiation on sympathetic and parasympathetic nerve endings and ganglia, a conclusion reached without benefit of laboratory experience.

On the basis of clinical experience, Rovello & Ferri (88) claim that pyridoxine will control the leucopenia following x-ray therapy.

Rekers, Coulter & Warren (89) tried to alter the course of radiation disease by transplanting bone marrow from an unirradiated dog to an irradiated one. The transplant did not prevent or even delay death. In the animals that survived, the transplanted bone did not survive at all, but was eventually entirely replaced by new bone growth.

Umanskiĭ, Varshavskiĭ & Kudokotsev (90) attempted to find drugs which

would act as a sensitizer to radiation. Using the re-growth of amputated amphibian limbs as a test object, they found that fluorescein was quite effective, and suggest that it might be quite useful in the x-ray treatment of tumors. Schreck (91) made an extensive morphological study of cells exposed to x-rays and to nitrogen mustards. They found that if there is any difference between the action of these two agents, it must be quite slight. De Bruyn and Robertson come to the same conclusion after studying the lymphatic nodule of the rabbit following the application of these two agents.

There has been a good deal of work recently on the part played by infection in the radiation syndrome in mammals, and it seems clear now that it plays a part, although probably not a very dominant one. Miller, Hammond & Tompkins (139) made a very thorough study of this in mice by culturing different organs from the mice at different times after x-irradiation. They found positive cultures in a high percentage of the mice, and the organisms were the same as those normally found in the intestinal tract of these animals. In many instances there was only one type of organism found in an animal, so they conclude that the organisms must be growing in the blood and tissues, since if such were not the case a wide variety of different organisms would be found. This seems reasonable, since it has been known for many years that animals subject to radiation are less able to withstand infection. It is significant also that bacteremia occurred most frequently in their mice during the period of greatest mortality. It should be stressed that this does not necessarily mean that the mice died as a result of the bacteremia, since many died in which it was not possible to demonstrate any infection. This work is confirmed by Bennett *et al.* (92), but these investigators did not find as high a percentage of infected animals.

Following up this work, Howland and co-workers (93) have made an extensive test of the effect of antibiotics on the radiation syndrome. They find aureomycin to be by far the most effective. Using this on rats, dogs, and one human they find first that the symptoms of acute radiation sickness such as vomiting and diarrhea seem to be almost completely relieved by prior treatment. In the case of lethal doses of x-ray, life may be prolonged 5 to 7 days in rats, and when they die it is a type of death not typical of radiation death in this species. The present indication is that the percentage mortality is also decreased. Similar results have been obtained by Miller, Hammond & Tompkins (140) using streptomycin and penicillin on mice, but observing only that there was somewhat of a reduction in mortality.

These results are in complete accord with those of Bennison & Coatney (94) who infected chicks with malaria and found a much higher count of infected red cells in chicks that had been x-irradiated. Also, Kohn (95) tested the ability of rats to produce antibodies following x-irradiation and found it to be lowered. Jacobson *et al.* (96) confirm this and further find that antibody formation is reasonably well maintained provided some part of the body such as the spleen or appendix is protected from the radiation. Emmett (97), confirming earlier work, found that bacteria can withstand enormous doses of

radiation with little change in structure or function. This is in apparent contradiction to the work of Hahn, Hoas & Wilcox (141) who found that mosquitoes fed P^{32} were able to arrest the development of malaria parasites in the salivary glands. In the absence of knowledge of the actual amount of radiation received it is not possible to say what the dose of radiation to the organism was, but it is safe to guess that it was low. It must then be assumed that the radiation affected the gland in such a way that it became an unfavorable medium for the development of the organisms. This is a field which would bear further exploration.

There seems to be an increasing conviction on the part of most investigators that irradiating one part of an animal can have profound effects on other parts. Recent concrete evidence for this belief has come from the work of Van Dyke & Huff (98) who irradiated one member of parabiotic twins in rats. They found first that the irradiated twin could stand a much higher dose of radiation than a normal rat, an interesting but perhaps not too surprising result. Much more interesting is the finding that there was extensive epilation both on the irradiated and the non-irradiated twin. Whether the non-irradiated twin gains a toxic substance or loses a beneficial one has not been determined. Another important piece of evidence in this connection is that by Jolles (99) who irradiated two small areas of skin in humans at varying distances apart. When the two treated areas were quite close together, the reaction in each was much more severe than when they were widely separated. He attributes this to the formation of a diffusible substance within the irradiated tissue.

Allen and his group (100) have further extended their work on the anti-coagulant in blood following x-irradiation. They have not yet definitely identified it as heparin, but describe it as heparinoid. In an *in vitro* study of coagulation in heparinized rabbit blood, Haley & Stolarsky (101) conclude that the coagulant action of various dyes, including toluidine blue, is not by inhibition of heparin. There may be an important species difference here since Rosenthal & Benedek (102) report that the hemorrhagic response in the rabbit is quite different from that in the dog or guinea pig, in that no free or excess heparin could be demonstrated in the blood following x-irradiation, and toluidine blue did not prevent the increased clotting time. Cronkite (103) made observations on goats and swine exposed at Bikini and concluded that a hemorrhagic syndrome can develop without the appearance of a prolonged clotting time and without a hyperheparinemia. One is tempted to wonder whether laboratory conditions in the South Pacific are comparable to those in Chicago.

There continues to be a great deal of interest in the hematopoietic system following irradiation. Jacobson, Simmons & Block (104) succeeded in irradiating only bone marrow in mice using Sr^{89} , and showed that anemia fails to develop because of an intense ectopic erythrocytopenia in the spleen. This group (105) went on further to investigate the role of the spleen. They protected the spleen during the total body x-irradiation of mice and found

that not only was the spleen normal, but the bone marrow and lymph nodes showed normal cellularity eight days after irradiation, whereas control bone marrow and lymphatic tissue was destroyed. This result could lead to some interesting speculation. Carter (106) found that the weight of the spleen in mice gives an accurate indication of the amount of radiation received, but the ratio of red to white pulp remains unchanged.

Davis and co-workers (107) find an increased bilirubinuria in bile fistula dogs exposed to x-rays and interpret this to mean an increased destruction of red cells. However, the red cells in the circulating blood appeared normal in every respect, and it took enormous doses of radiation to cause any hemolysis of red cells *in vitro*. A possible explanation of this apparent contradiction may be found in the experiments of Goldschmidt *et al.* (108) who developed a new method for measuring red cell fragility and found that rats, after a dose of only 500 r of x-rays, show an increased fragility within 4 to 12 hr. Hennessy & Huff (109) developed a quantitative method for measuring damage to hematopoietic tissue by the rate of uptake of radioactive iron. Schack & MacDuffee (110) find that if the bone marrow is made hyperplastic by exposure to low oxygen tensions for some time before (but not during) x-irradiation, the erythroid elements of the mouse are better able to withstand the exposure.

Radiation cataracts are among the most obvious and troublesome of the long term radiation effects. These are starting to appear in the Japanese exposed in the atomic bombings (111) and more may be expected. Abelson & Kruger (112) give a preliminary account of the cyclotron induced cataracts, and conclude, in agreement with experimental work on mice, that neutrons are especially effective in producing cataracts. Cogan (113) discusses the development of cataracts incident to x-ray therapy.

Several excellent histological studies have been published. Warren & Dixon (114) give a complete account of the effect of injecting P^{32} into chick embryos. Knowlton *et al.* (115) give an account of the β -ray burns suffered by four men at one of the atomic bomb tests. Goldberg, Chaikoff, Lindsay & Feller (116) give a detailed account of the morphological changes in the thyroid following I^{131} treatments. Gastaldi (117) gives an account of the changes following section of the sciatic nerve in rabbits and subsequent chronic x-irradiation of that leg. Burstone (118) gives a complete account of the morphological changes in teeth following x-irradiation. Smith, Svihla & Patt (119) observed directly the effects of x-irradiation on the capillary circulation in the bat's wing, and found that it took enormous doses of radiation to cause any visible effect. Bond *et al.* (142) found that when rats were irradiated in the abdomen only, the lethal gram-roentgen dose was about half the dose required when other parts of the body were irradiated. Kimeldorf *et al.* (120) found that rats subjected to vigorous exercise following irradiation were more likely to die, and Jennings (121) found that rats on a low protein diet were more susceptible to radiation. Ellinger & Barnett (122) studied the effect of dose fractionation on the lethal effect in rats and conclude that there

is optimum fractionation for producing death just as there is for tumor destruction.

There continues to be considerable interest in the carcinogenic effects of x-rays. Furth (123) finds that some strains of mice exhibit ovarian tumors in 100 per cent of the irradiated individuals, even with rather small doses. He further finds (124) that pregnancy has no effect on this tumor induction. Koletsky, Bonte & Friedell (125) find P^{32} a very carcinogenic substance. Warren (126) has predicted that there will be an increased incidence of leukemia and ovarian tumors in Japanese exposed in the atomic bombings, but none have appeared yet.

Figge (127) continues to report an increased tumor incidence in mice treated with methylcholanthrene because of the influence of cosmic rays. It is very doubtful if his results would stand statistical analysis, and, indeed, George *et al.* (128) tried to repeat his observations and failed.

Kaplan (129) has obtained important evidence that lymphoid tumors may not necessarily be due to a direct action of the radiation on the cell in question, but may be caused by an indirect effect. Kaplan & Murphy (130), in a study of tumor transplants, concluded that radiation may produce its effect on a tumor partly by changing the cell type of the tumor. Koller (131) studied the similarity between x-rays and nitrogen mustards in their effects on tumor growth. He concludes, among other things, that probably the primary effect of the radiation is on the cytoplasm of the cell, which in turn affects the nucleus. Kirschbaum, Shapiro & Mixer (132) found that there is a synergistic action of estrogenic hormone and x-rays in inducing thymic lymphosarcoma. Elson & Lamerton (133) studied the effect of the protein content of the diet on the response of implanted tumors to x-rays. They concluded that there are two processes involved, (a) the initial inhibition of the tumor growth, and (b) the elimination of the inhibited tumor. The first of these is favored by a low protein diet, and the second by a high protein diet. Hoch-Ligeti (134) found that x-rays may either accelerate or retard the tumor induction in the liver caused by feeding *p*-dimethylaminoazobenzene to rats, depending on the dosage of x-rays used.

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DEVELOPMENTAL PHYSIOLOGY

BY JOHN RUNNSTRÖM AND TRYGGVE GUSTAFSON

*The Wenner-Gren Institute for Experimental Biology, The University of Stockholm,
Stockholm, Sweden*

This review will deal mainly with the work carried out with the aim of elucidating morphogenesis. Within this field, the purely biological methods of separating or transplanting embryonic parts still play an essential role. They give fundamental information about the relationships between different embryonic regions. The introduction of additional methods and points of view from biochemistry and cell physiology has, however, given a new impetus to the study of morphogenesis. The synthesis of specific proteins seems, at present to be a major problem in this field [see Northrop's discussion (1)]. Chemical differences found in desoxyribonucleic and ribonucleic acids from different sources support the view that these compounds may also be carriers of type or organ specificity [see Chargaff and co-workers (2 to 5)]. The results obtained by Vendrely & Vendrely (5a) and by Mirsky & Ris (5b) concerning the constancy of desoxyribonucleic acid content of the nuclei of a species also point to the genetic importance of this substance. With a biological method, Mazia (5c) obtained results pointing to species differences of desoxyribonucleic acid.

Recent cell research emphasizes the role of particulate inclusions in the cytoplasm [see Brachet (6)]. It seems probable that protein synthesis in cytoplasm is bound to such ribonucleic acid-containing particles which can be demonstrated *in situ* by suitable methods (7, 8). Evidence supporting this view has also been produced, for example, by the addition of labelled amino acids to suspensions of particles from liver (9) [see also 10, 11]. In the mitochondria, biochemical research has been able to establish the occurrence of a highly organized mosaic of enzymes (12).

A self-perpetuation of ribonucleic-containing particles has often been postulated. Certain results obtained by genetic methods favor the assumption of autonomous cytoplasmic particles (13, 14, 15) or "plasmagenes."

The mechanism of differentiation is discussed on the basis of the plasmagene concept in Spiegelman's stimulating article (16). The differentiation is considered to be the outcome of a competitive interaction between different enzyme-producing plasmagenes.

Experiments on enzyme adaptation in yeast formed the basis of Spiegelman's discussion. The experiments showed that according to the substrate present a modification of the enzyme occurred against a constant genetic background [for a discussion of enzyme adaptation see also Monod (16a)].

In Spiegelman's opinion the plasmagenes are primarily gene products. It is therefore doubtful whether the designation "plasmagene" is appropriate for the units conceived of by this author. The term should strictly be reserved for such cytoplasmic units which, like the nuclear genes, present con-

tinuity and mutability. It remains questionable, however, if any such units exist besides the plastids, the virus, and the central apparatus [see Schultz (16b)].

DEVELOPMENT OF THE GENITAL CELLS

The present state of the germ line concept has been ably reviewed by Nieuwkoop (17) with respect to vertebrates. The presumptive primordial germ cells seem to have a mesodermal origin in the Urodeles, but probably derive from the central entoderm in the Anura. According to experiments on Urodeles, the final differentiation of the germ cells is dependent upon influences from the dorso-caudal entoderm.

The results obtained by Brauer (18) with ultraviolet irradiation (wavelength: 2537 Å) on the posterior part of the early blastoderm of the pea beetle are in keeping with the early segregation of germ material in insects.

A valuable contribution to the cytochemistry of both oögenesis and spermatogenesis in *Parascaris equorum* was provided by Pasteels (19). Ribonucleic granules appear within the cytoplasm, having been introduced into the egg by the spermatozoön. In the mitoses of segmentation these ribonucleic granules are condensed into polar caps. In the cells of the germ line the caps are distinguished by their greater density and closer relations to the cortex.

The development of the female sex cell in the ovary constitutes, no doubt, a very important stage in the establishment of the organization of the egg. The cytochemistry of oögenesis has been studied by Raven (20, 21) in *Limnaea stagnalis* and by Fauré-Frémiet *et al.* (22) in *Glomeris marginata*, [see also (23, 24)]. Dalcq & Seaton-Jones (25) were able to show that the oöcytes of rat, mouse, and rabbit, have a bilateral structure recognizable by a layer of basophilic granules on one side and a layer of vacuoles on the other. The former seems to indicate the dorsal and the latter the ventral side of the developing embryo. Goldschmidt (26) reviews earlier and recent evidence of gene actions upon the egg before fertilization [see also Fankhauser (27)].

PHYSIOLOGY OF FERTILIZATION AND CLEAVAGE

Some rather comprehensive reviews deal with different aspects of fertilization. Tyler (28) regards the interaction between eggs and spermatozoa from the point of view of specificity. Certain of the substances on or within the eggs and spermatozoa interact in the same way as antigen and antibody. The specificity of interaction of these substances explain the species specificity found during fertilization. Bielig & Medem (29) give an account of the chemical nature and the mode of action of the "gamones." Runnström's review (30) refers not only to the nature of the interacting substances, but also to the changes in structure and metabolism occurring subsequent to the activation of the egg. He regards tentatively the removal of certain enzyme inhibitors as the initiating reaction in fertilization [see also (31)]. Finally

Rybak (32) discussed the "gamone" problems from a biochemical point of view.

The jelly coat surrounding the sea urchin eggs is the source of those factors which cause a species specific agglutination and an activation of the spermatozoa. Owing to space limitation, a number of papers dealing with the chemical composition and physiological activity of the jelly substance (32 to 47) can only be mentioned here as references.

A species specific factor complementary to the agglutinating factor of the jelly has been postulated to be present at the surface of the spermatozoa [sperm receptor, sperm antifertilizin (28)]. Extracts obtained by several methods were considered to contain the sperm antifertilizin. According to Hultin (48, 49), however, the extract exerts an unspecific action on the jelly coat and the egg surface by virtue of its content of desoxyribonucleoproteins. The basic protein moiety of these is considered to be the active part [for a discussion of this question see (50, 51)]. It is of interest that these basic proteins evoke the first steps of parthenogenesis (52).

When the fertilization of the sea urchin egg is watched with dark ground illumination, a cortical change can be directly observed (30). Rothschild & Swann (53) raise the question whether the dark ground change is associated with the block to polyspermy. This seems to be possible in view of the low probability of successful collisions between spermatozoa and egg. The diffusion of the acting substance is more intracellular than cortical (54). The same initial cortical changes which favor the differentiation of the fertilization membrane also act as a block to polyspermy (46).

The fertilization membrane in sea urchin eggs has a double origin from (a) the preformed vitelline membrane and (b) matter expressed from the cortex (45, 55). The first observation to this effect was reported by Motomura (56). Costello (57) made a careful study of the relations of the plasma membrane, vitelline membrane, and jelly in the egg of *Nereis limbata*.

Addition of calcium to homogenates of *Paracentrotus lividus* eggs prepared in calcium-free sea water causes an outburst of oxygen-consumption and acid formation. The viscosity of the homogenate increases two to three-fold. An oxidation of protein-bound sulfhydryl groups seems to be involved. Addition of papain to the calcium-free homogenate also brings about acid formation and viscosity increase (58, 59). A report on the action of calcium and ATP (adenosinetriphosphate) on the colloidal properties of the cytoplasm of intact or broken up sea urchin eggs is given by Runnström & Kriszat (60). The changes in respiration occurring upon the fertilization of the sea urchin egg have been further analyzed in interesting papers by Borei (61, 62), Borei & Lybing (63) and by Rothschild (64).

Following Bataillon's pricking method, Shaver (65) injected particles from frog blood, testis, or blastula into virgin frog eggs. Small granules obtained at high speed centrifugation ($18,000\times g$) of homogenates gave a lower percentage of parthenogenetic larvae than larger granules sedimenting at $3,000-6,000\times g$. The higher enzyme content of the larger granules may account for the difference.

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A species specific factor complementary to the agglutinating factor of the jelly has been postulated to be present at the surface of the spermatozoa [sperm receptor, sperm antifertilizin (28)]. Extracts obtained by several methods were considered to contain the sperm antifertilizin. According to Hultin (48, 49), however, the extract exerts an unspecific action on the jelly coat and the egg surface by virtue of its content of desoxyribonucleoproteins. The basic protein moiety of these is considered to be the active part [for a discussion of this question see (50, 51)]. It is of interest that these basic proteins evoke the first steps of parthenogenesis (52).

When the fertilization of the sea urchin egg is watched with dark ground illumination, a cortical change can be directly observed (30). Rothschild & Swann (53) raise the question whether the dark ground change is associated with the block to polyspermy. This seems to be possible in view of the low probability of successful collisions between spermatozoa and egg. The diffusion of the acting substance is more intracellular than cortical (54). The same initial cortical changes which favor the differentiation of the fertilization membrane also act as a block to polyspermy (46).

The fertilization membrane in sea urchin eggs has a double origin from (a) the preformed vitelline membrane and (b) matter expressed from the cortex (45, 55). The first observation to this effect was reported by Motomura (56). Costello (57) made a careful study of the relations of the plasma membrane, vitelline membrane, and jelly in the egg of *Nereis limbata*.

Addition of calcium to homogenates of *Paracentrotus lividus* eggs prepared in calcium-free sea water causes an outburst of oxygen-consumption and acid formation. The viscosity of the homogenate increases two to threefold. An oxidation of protein-bound sulfhydryl groups seems to be involved. Addition of papain to the calcium-free homogenate also brings about acid formation and viscosity increase (58, 59). A report on the action of calcium and ATP (adenosinetriphosphate) on the colloidal properties of the cytoplasm of intact or broken up sea urchin eggs is given by Runnström & Kriszat (60). The changes in respiration occurring upon the fertilization of the sea urchin egg have been further analyzed in interesting papers by Borei (61, 62), Borei & Lybing (63) and by Rothschild (64).

Following Bataillon's pricking method, Shaver (65) injected particles from frog blood, testis, or blastula into virgin frog eggs. Small granules obtained at high speed centrifugation ($18,000\times g$) of homogenates gave a lower percentage of parthenogenetic larvae than larger granules sedimenting at $3,000-6,000\times g$. The higher enzyme content of the larger granules may account for the difference.

Harding (66) pricked virgin eggs of *Rana pipiens* in the presence of heparinized frog blood. The percentage of divisions was found to be lower than in eggs which have been pricked in blood plus Ringer solution. According to Heilbrunn & Wilson (67), heparin blocks cell divisions in *Chaetopterus* eggs. The same authors (68) made a careful study of the viscosity changes occurring between fertilization and the first cleavage.

Metz & Foley (69) studied a nonconjugating stock of *Paramecium* (CM) and found it capable of inducing activation (macronuclear break-down, meiosis, and loss of mating activity) in conjugating stocks.

BIOCHEMICAL APPROACH TO MORPHOGENESIS

Respiration.—The rate of respiration in fertilized sea urchin eggs increases exponentially up to a certain stage (early blastula); thereafter the curve forms a plateau, but shortly before gastrulation the respiration begins to increase as a linear function of time. Borei (61) has confirmed these data and shown that on the whole the same type of curve applies to the starfish egg (70). Tuft (71) found an analogous sequence of three periods to exist also in the egg and embryo of the insect *Rhodnius prolixus*. The different periods of oxygen consumption seem to be correlated to morphogenetic changes. The changes of rate in respiration in development of *Urodeles* and *Anura* and the corresponding changes in activity of some respiratory enzymes have been reviewed by Boell (72). The question of regional differences in respiratory rate is also subject to a thorough discussion by this author. When correction is made for the amount of inactive material present, the respiratory rates of different parts of the amphibian gastrula are identical. Intensity of respiratory metabolism and inductive action are thus not necessarily associated [see also Holter (73)].

Child (74) finds definite patterns of indicator oxidation in *Triturus* development. The indicator solution surrounding the embryos were kept in a reduced state and the "intracellular oxidation" of the dye (Janus green, methylene blue) was observed. In the gastrula stage, roughly the same regional differences seem to prevail as those indicated by the noncorrected values of respiratory rate.

By means of the Cartesian diver technique, Boell & Nicholas (75) found an increase of Q_{O_2} in the rat egg from 29 at the one-cell stage to 42.5 at the eight-cell stage.

Adenosinetriphosphate (ATP) and adenosinetriphosphatase.—Barth & Jaeger (76) have ascertained that in frog eggs the amount of adenosinetriphosphate remained unchanged from cleavage until the early neurula stage. ATP was broken down under anaerobic conditions. In the cleavage stage, however, this breakdown was relatively small and development proceeded. In the gastrula stage a stronger ATP-breakdown occurred and the development stopped. It is implied that ATP probably constitutes the energy source for gastrulation. This was also confirmed by observations on hybrid gastrula with a decreased capacity for maintaining adenosinetriphosphate in

the phosphorylated state [see also (77)]. Further evidence about the role of adenosinetriphosphate as an energy source for differentiation was obtained from experiments on a composite ascidian, *Symplegnia* (78, 79). The regeneration of zooids from stolons was associated with a strong increase of the adenosinetriphosphatase activity, whereas this was very low in the isolated stolon. Differentiation is here independent of growth. The changes in adenosinetriphosphatase activity are thus connected with differentiation (including cell migration) and not merely with growth.

Lindberg (80) studied the exchange of the isotope P^{32} between orthophosphate added to the sea water and ATP present in the sea urchin egg. In the unfertilized egg, the turnover of ATP can only be demonstrated in a very thin layer of the surface, the thickness of which was roughly estimated to be 0.02 to 0.05 μ . The equilibrium is soon established between the surface layer and the surrounding medium. A turnover of ATP also takes place in the surface of the fertilized egg, but labelled ATP slowly diffuses into the egg. The penetrating ATP seems to be trapped in such a way that no equilibrium with the inorganic phosphorus is established in the early development. In the stages of initial differentiation, however, an equilibrium is approached. This signifies that the participation of ATP in the metabolism of the inner cytoplasm begins to be intensified in these stages. In agreement with these results, Gustafson & Hjelt (81) found the adenosinetriphosphatase activity in the sea urchin embryo to be relatively low up to gastrulation. After this stage an increase to at least twice the initial activity occurs. Vegetalizing concentrations of lithium impede this increase of adenosinetriphosphatase activity.

Other enzymes.—The alkaline phosphatase shows a course of development similar to that reported for adenosinetriphosphatase, but in this case the increase is only somewhat delayed, rather than checked, by the presence of lithium (82). [See also Mazia *et al.* (82b)].

According to Augustinsson & Gustafson (83), choline esterase activity in the sea urchin egg appears in the blastula stage just before hatching. This is the stage of commencing ciliary movements. A second step in choline esterase formation coincides with the development of ciliary bands and other ciliary structures in the ectoderm. This step is checked by lithium as a consequence of the inhibitory effect of this ion on the differentiation of ectoderm. A third step of activity increase is mainly associated with the beginning contractility of the intestine. This step does not seem to be suppressed by lithium. The lithium-effect on the choline esterase development is probably an indirect one. The enzyme is considered to be synthesized as a response to the formation of acetylcholine by a kind of enzyme adaptation. The earlier work on choline esterase formation in amphibian development has been reviewed by Boell (72).

According to Fitzgerald (84), no activity of alkaline phosphate is detectable in the grasshopper egg until after the twelfth day of development. At this point a rapid increase of activity sets in. No further increase occurs

in the diapause stage, but activity recommences upon the resumption of development.

Nucleic acid, proteins.—The behavior of the nucleic acids during the course of the development of the sea urchin egg has been reinvestigated by Villee *et al.* (85). There was an increase in desoxyribonucleic acid (DNA) with time, whereas the ribonucleic acid (RNA) remained essentially constant until the 72-hour stage (85). Experiments with P^{32} demonstrated that DNA was not formed at the expense of RNA (85). According to Mazia (86), the desoxyribonuclease does not increase during the first 40 hr. of development. The enzyme seems to be stored in the cytoplasm, but parallel to the increase in DNA, an increasing amount is bound to the nuclei. Glycine labelled with C^{14} on the alpha carbon was used by Friedberg & Eakin (87) in experiments on the incorporation of this amino acid in the proteins of developing embryos of the Pacific tree-frog, *Hyla regilla*. Owing to the low permeability of the skin, particularly in embryos beyond the gastrula stage, the main experiments were carried out on embryos cut in two pieces. An increasing incorporation of the radioactive carbon into proteins was found from the beginning gastrula stage through the early larval stages. This probably indicates an increased protein synthesis associated with differentiation and growth. The interesting problem of regional differences was also attacked in this research. Consistent differences between dorsal and ventral halves were not found in the gastrula stage. Conversely, the incorporation of C^{14} in proteins was definitely found to be stronger in the dorsal than in the ventral half of neurulae.

Gustafson & Hjelte (81) have studied the metabolism of 18 amino acids in the early sea urchin development. The amino acid composition is remarkably constant until gastrulation. During gastrulation a more or less distinct drop in the content of various amino acids appears, while glycine shows an increment. For certain amino acids no clear changes could be demonstrated. The amino acids seem to change less at the beginning of differentiation of lithium-treated embryos, than of normal embryos. The free amino nitrogen is reduced from 21 to 17.6 per cent during gastrulation in normal embryos. This change cannot be demonstrated in the presence of lithium. The total (Kjeldahl) nitrogen is, however, constant in both cases. This may indicate that free amino nitrogen disappears perhaps by peptide formation during normal development but not in the presence of lithium. Free glutamine found to be present in earlier stages disappears almost entirely at normal gastrulation and at comparable stages in the presence of lithium.

Serological studies [Perlmann & Gustafson (88)] failed to demonstrate the appearance of new antigens before the early gastrula stage. Between this and the 48-hour stage, new components appear, both during normal development and in presence of lithium.

Hörstadius & Gustafson (89) and Hörstadius (90) have studied the influence of certain substances on the course of development of isolated animal halves of the sea urchin egg. A number of amino acids conferred a more vegetal character upon the fragments (vegetalization). Lower temperatures (11

to 15°C.) favor the opposite change (animalization), whereas higher temperatures (21 to 26°C.) cause an increased percentage of vegetalized fragments.

According to Lindahl, Swedmark & Lundin (91), the animalization of unfertilized eggs of *P. lividus* following the exposure to thiocyanate-ions in calcium-free sea water under aerobic conditions is decidedly inhibited by light. Eggs of females from one locality were more prone to animalization than those from other localities. The proteins of the former eggs proved to be more soluble in ice-cooled 0.54 *M* sodium iodide than was the latter. It is suggested that thiocyanate-ions cause a swelling of the proteins involved in animalization. This probably favors the oxidation of certain groups which are protected in the normal dehydrated state. In addition to the sulfhydryl-group, tyrosine and tryptophane may be concerned in these oxidation processes.

Ranzi and co-workers have continued their studies on the influence of lithium- and thiocyanate-ions on protein solutions obtained in extracts from eggs. The present paper (92) deals with proteins from sea urchin eggs. Lithium and other vegetalizing agents increase the viscosity of the protein fractions having fibrous molecules. Thiocyanate-ions and other animalizing agents, on the other hand, decrease the viscosity of the same fractions. The vegetalization would thus follow upon a polymerization, and the animalization upon a depolymerization of the fibrous proteins present in the egg cytoplasm. Raven's (93) results on *Limnaea* eggs favor the view that lithium ions primarily affect the water equilibrium between various components of the egg.

The reviewers consider also that such colloidal changes may be the primary effects of thiocyanate and lithium ions. The latter is probably a competitor with potassium in certain high molecular compounds. The primary changes caused by the ions interfere, however, with anabolic processes which produce certain enzymes or other specific substances, [see (94) for discussion]. As demonstrated by the work of Lindahl *et al.* (91) the animalizing ions are active only under certain exacting conditions.

According to Child (95), the action of lithium on eggs of *Strongylocentrotus purpuratus* is not specific, but entodermization and exogastrulation are obtained also by sodium azide and other inhibitory substances. Rulon (96) demonstrates the modification of developmental pattern in the sand dollar with maleic acid, an inhibitor of the succinic oxidase.

Explantation.—In a very interesting paper, Spratt (97) demonstrated that explanted chicken blastoderm undergoes morphogenesis characteristic of the first two days of incubation on a buffered Ringer solution plus *D*-glucose. This hexose could, however, be substituted by *D*-mannose, *D*-fructose, *D*-galactose, and *D*-maltose. The relative activity of these is: glucose = mannose > fructose > galactose = maltose. Taylor & Schechtman (98) show that yolk extracts contain, besides sugar, macromolecular nonenzymatic factors which support early differentiation in chicken embryo. The cessation of the *in vitro* development of blastoderm is due to circulatory failure.

According to Devillers (99), explanted trout blastoderm undergoes no

growth, differentiation, or gastrulation in Holtfreter saline. After the addition of glucose, however, the morphogenesis proceeds to a certain extent, but the form of the resulting embryos is abnormal. The physico-chemical properties and the role of the cortex in the developing trout egg are discussed in a separate paper by this author (100).

MORPHOGENETIC RELATIONSHIPS BETWEEN DIFFERENT GERM REGIONS

Echinoderms.—Hörstadius (90) has made a survey of the experimental morphogenesis of the sea urchin. It seems firmly established that two different principles, the animal and the vegetal, must interact in a balanced way to bring about the normal differentiation of the sea urchin embryo. The interactions are most readily considered to be mediated by substances formed at an animal and a vegetal center from which these substances spread by diffusion, thus forming two overlapping gradients. These gradients do not correspond to gradients of oxidative metabolism. The animal and vegetal substances are believed by the reviewers to compete for macromolecules or organized particles on different levels along the axis, thus giving rise to diversities possibly in a manner recalling enzyme adaptation (94). The determination of the main embryonic areas is already accomplished in an early blastula stage before any manifest differentiation of these has occurred [see Hörstadius (90) and Gustafson (94)]. The determination process implies a latent differentiation brought about by the formation of a limited number of specific molecules present in definite proportions, whereas manifest differentiation is due to a strong propagation of these specific molecules.

Hörstadius (101) combined older vegetal halves of the sea urchin embryo with younger animal halves and vice versa. Even if the difference in age were 14 to 17 hr., the halves were able to interact so that a normal balance was established between the animal and vegetal differentiation. The animal and vegetal agents thus continued their activity even after the period of definite determination of the embryonic areas.

Bilateral symmetry seems to be already established before the fertilization of the sea urchin egg (102), but definite determination only occurs in the blastula stage (90, 102).

Hörstadius *et al.* (103) have tested whether the vegetal gradient field of the sea urchin egg is localized in or dependent upon the endoplasm, as had been assumed by Dalcq. A considerable reduction of the amount of endoplasm did not disturb the balance of the gradient system. The eggs developed after fertilization into normal larvae.

Vertebrates.—Conversely, in amphibia, the cephalo-caudal gradient is dependent upon the endoplasm [see Pasteels' survey of the subject (104)]. A reversal of the localization of the vegetal and animal endoplasms with respect to the cortex reverses the cephalo-caudal gradient, the cephalic pole always being nearest to and the caudal pole most remote from the vegetal endoplasm [cf. (105)]. The dorso-ventral gradient has its maximum intensity in the center of the grey half moon. The position of this gradient field be-

comes definitely fixed at the moment of the copulation of the pronuclei [see (104)]. Yamada (105a) isolated the ventral marginal zone of the early gastrula of *Triturus pyrrhogaster* and cultured it in Holtfreter solution. A differentiation of blood island, blood vessels, mesothelium, and nephric tubules was observed. If, however, the isolated zone was subjected to treatment with an ammonia solution and then transferred to Holtfreter solution, the material gave rise to notochord and muscle tissue besides nephric tubules, whereas the development of the blood island, mesothelium, and blood vessels was almost completely suppressed. The author designates the change occurring upon ammonia treatment as "dorsalization." It is obvious that these results are closely related to those studied by the Swedish workers (89, 90, 91, 94) on sea urchin eggs under the name of animalization and vegetalization.

Several papers by Dalcq and his school are devoted to an analysis of the early determination in the egg of *Urodeles* (106 to 111). The concept of physiological competition introduced by Speigelman has been applied by Dalcq (112) to different problems of morphogenesis. In a comprehensive article, Nicholas (113) discusses the "form changes during pre-gastrular development." The yolk endoderm seems to have various inductive actions, e.g., in the formation of the heart, the splanchnopleure, stomodaeum, and the gills, and may possibly influence the formation of both the hypophysis and the thyroid. Pasteels (114) analyzes the localization of different parts of the endoderm and the gastrulation movements in *Xenopus laevis*. Stabbleford (115) isolated the vegetal hemisphere of *Amblystoma punctatum*. No intrinsic capacity for morphological differentiation was found, however, except for the formation of an invagination groove. On the whole, the capacity for regulation seems to be extremely limited in *A. punctatum* when compared with that of other amphibians.

In a stimulating review, Holtfreter (116) discusses the mechanism of embryonic induction. Summarizing the present evidence he arrives at the conclusion that neural induction in isolated ectoderm may be caused by a process of mild cytotoxicity. This process may cause a release of an agent *X* from a compound *XN*. Once liberated, the *X*-agents favor further release of *X*. This agent remains active during the subsequent stages. The structural element *N*, probably of a protein nature, becomes a constituent of the cell membrane. It thus gives the cell new kinetic properties characteristic of the neural cells. The *X*-factor is also released when killed tissue or a poisonous substance is inserted between endo- and ectoderm. In a living organizer, the factor *X* is already present in a free state. It is transmitted into the adjacent ectoderm causing there the same changes as those produced by mild cytotoxicity. These views are admittedly simplified. They do not account for the purely cephalic character of the inductions brought about in explants. They bring, however, organizer action in relation to phenomena fruitfully approached by cell physiology. Holtfreter considers the possibility that the neuralization involves a kind of induced somatic mutation of self-propagating plasmagenes. Weiss (116a) has followed the finer cytological changes which

occur at the induction of lens upon intimate contact between ectoderm and subjacent retinal cells. The interesting discussions by Dalcq (117), Rotmann (118), and Eakin (119) can only be mentioned here as references.

Toivonen's results (120) with heterogenous inductors support the assumption of at least two inducing agents. He submitted guinea pig liver and kidney tissue to chemical fractionation. The head inductor present mainly in liver appears in two different fractions, one containing the nucleoproteins, the other the fatty acids. This factor is thermostable, whereas the trunk inductor, present mainly in the kidney, is thermolabile and insoluble in organic solvents. The organ difference with respect to the distribution of the inductors was not found in parallel experiments with bovine liver and kidney (121). The inducing capacity of the liver was, however, superior to that of the kidney tissue.

According to Devillers (122), trout embryos without notochord may develop after appropriate removal of invaginating material in the early gastrulae. Nevertheless, a somewhat atypical primordial nervous system seems to develop in these larvae without any notochordal induction. Mesoblastic induction may suffice or the nerve primordium might have the capacity of self-differentiation in this material. Normal stretching occurs also in embryos without notochord. Conversely, notochordectomy carried out in an embryo with a fully-formed neural plate caused a complete failure of antero-posterior stretching in *Amblystoma mexicanum* (123). The notochord also proved necessary for the normal metameric cartilage formation.

Valuable work has been carried out on the localization and morphogenetic capacity of the neural crest (124, 125) as well as on the inductive influence exerted by the Wolffian duct on the mesonephros (126, 127).

Spiralia.—A great difference has earlier been supposed to exist between regulatory and mosaic development. Recent work, however, tends to remove the alleged barriers between these types. This follows, for example, from a review by Raven (20) which deals mainly with the experimental work on *Limnaea stagnalis* carried out by him and his co-workers. He considers that the "germinal localizations" in *Limnaea* and similar objects are founded on relative, rather than on absolute, differences between the germ regions. The existence of a gradient field with its maximum at the animal pole has been demonstrated in lithium experiments. From these it could also be inferred that the pattern of determination is not yet irrevocable at the 24-cell stage [For further details see (128, 129, 130)]. Lehmann's (131) studies on *Tubifex* give fundamentally the same results. With different experiments, i.e., orientated centrifugation of the eggs in maturation, epigenetic processes were demonstrated in the *Tubifex* egg. The formation of the somatoblasts, for example, is not yet irrevocably determined in the one- or two-cell stages. From an investigation on the polyembryony in an earth worm (*Allobophora trapezoides*), Omodeo (132) concludes that the mesodermal portions of the germ bands serve as organizers of the ectodermal portions.

Ascidia.—Complicated interactions have been revealed in the ascidian embryo, particularly by the work of Reverberi & Minganti (133, 134).

The anterior vegetal cells induce the formation of brain, sense organ, and palps in the parts developing from the anterior animal cells. The latter cells, on the other hand, are necessary for the development of the spinal cord, which is formed from a part of the material of the anterior vegetal cells. The posterior vegetal cells exert an inhibitory action on the formation of the brain. This inhibition is counteracted by the posterior animal cells. The interlocking actions demonstrated in the ascidian egg recall the conditions prevailing in the "regulatory" sea urchin egg.

Insects.—Hadorn *et al.* (135, 136) have transplanted different fragments of the imaginal disc of the male genital organ into the abdomen of host larvae. The further development of the fragments show that the larval genital disc is already divided into different areas, each of which give rise to a definite portion of the male genital apparatus. Fragments of single areas, however, are capable of regulation. The fragments differentiate at the expense of host material into elements of the species' characteristic normal form and size. The segregated areas have a field organization. The age of the host has a certain influence on the regulation of the grafted pieces. The lively mitotic divisions, prerequisite for the regulation processes, are possible only before the onset of the metamorphosis of the host larva. The homozygous mutant "spermatheca" modifies the development of the spermatheca and their ducts. According to Graber (137), the mutant characters could, however, be widely modified by exposure to different temperatures. The temperature-sensitive period was definitely limited, lasting for 24 hr. at 25 to 28°C. This period was always terminated before the onset of pupation.

As shown by Bodenstein & Abdel-Malek (138) the arista—a bristle-like appendage of the antenna—is transformed into an aristapedia in *Drosophila virilis* after exposure of certain larval stages to nitrogen mustard. The aristapedia is a leglike structure. All gradations are found, however, from a slightly modified arista up to a leg with end claw and typical leg bristles. In some cases antennal material was also changed into leg structures.

The arista *anlage* is thought to consist of two parts, the arista and the leg part. At a certain stage, the former assumes a higher mitotic rate and thus takes the lead in differentiation. However, if the treatment is applied at a certain stage it may reverse the growth potential. The leg part may now assert itself or take the lead. Accordingly, more or less complete aristopedias appear. The treatment with nitrogen mustard upsets the normal balance within the *anlage*. An effect on growth is probable in view of the fact that nitrogen mustard probably prevents the synthesis of desoxyribonucleic acid (139).

REGENERATION

The role of nerve supply for limb regeneration in amphibia is an interesting but, in certain respects, still controversial topic. Reference was made in a previous review (140) to Singer's careful work on the morphogenesis of the regenerating forelimb of adult *Triturus*. Extending the previous studies, Singer & Craven (141) show that removal of the nerves from the regenerate

before the thirteenth day of regeneration inhibits any further increase in volume and length. Furthermore, the mitotic activity was found to be blocked. If the regenerate is 13 days or older at the moment of denervation, differentiation and growth in length will occur, but volumetric increase is blocked in the denervated regenerate rate at any stage after operation. In a later paper, Singer (142) demonstrates that nerve fibers invade the epidermis of the regenerating forelimb in numbers considerably exceeding those found in the normal skin. The fibers are neither surrounded by Schwann cells nor by myelin sheath. Regenerates with a quantitatively reduced nerve supply were always found by Singer & Egloff (143) to be deficient in comparison with the control. A direct proportionality between onset and rate of regeneration to quantity of nerves available was not found. Rose (144) in his review, maintains that the nerve supply of the regenerating limb in amphibia is necessary for the dedifferentiation. Moreover, the nerve supply seems to shift the balance between growth and differentiation towards growth. In a further paper, Rose (145) presents quantitative data which are considered to prove the essential role of dedifferentiated epidermis cells for the blastema formation in regenerating *Triturus* limbs. Liebman (146), on the other hand, claims that the cells making up the core of the blastema are fibroblasts derived from similar elements of the stump. The effect of denervation on limb regeneration in urodele larvae was studied by Butler & Schotté (147). The denervation was carried out at different periods after the amputation. The neural influence proved to be essential for the early mobilization of the cells forming the blastema. At a "critical" period, 7 to 9 days after the amputation, the blastema assumed the capacity of differentiating slowly even after the removal of the nerve supply. After about the tenth day, finally morphogenesis was emancipated from the neural influence. Differentiation proceeds as rapidly as in normal regeneration although growth may be slightly retarded. A tendency towards autolysis always seems to prevail upon amputation. Blastema formation, however, checks this tendency.

Perri (148, 149) has induced supernumerary limbs in larvae of *Bufo vulgaris* by the implantation of perviously x-radiated apical parts of the head into the trunk of embryos at the tail bud stage. In this way, important information was gained about the extension of the anterior and posterior limb fields. Bateson's rule of mirror symmetry was found to be valid for double formations. Certain experiments seemed to indicate that diffusion of ribonucleic acid from the implant may play a role in the induction of the supernumerary limb (150).

Luther (151) replaced the skin from a part of the tail of larvae of *Salamandra maculosa* by belly or limb skin from larvae of the same age. After some time, the tail was amputated in the transplant region. The shape of the developing regenerate was influenced by the character of the transplant. For example, rudimentary fingers were recognized on tails to which limb skin had been grafted. If the animals had been subjected to a dose of x-rays sufficient to stop cell divisions (1,500 r) the host tissues did not participate in regeneration, but the transplanted limb tissue now gave rise to a complete

limb with skeleton, muscles, fingers, etc. The results show that the transplants retain their original morphogenetic potentialities. The differentiation of the single cells is, however, very versatile, as the transplanted skin was able to give rise to all the different tissues of the limb. The important work of Weiss & Hiscoe (152) on the mechanism of nerve growth may also be referred to in this context. An extensive experimental study of the behavior of constricted nerves proved that new protoplasm of the nerve is formed in the nucleated part of the cell body. A centrifugal convection of axoplasm takes place also in mature fibers. In this way, catabolized cytoplasmic systems, especially proteins, are replaced. Reference can only be made here to a number of interesting papers concerning regeneration in *Stentor* (153, 154, 155) and in different invertebrates (156 to 160).

NUCLEAR CONTROL OF DEVELOPMENT

The action of the genes on the cytoplasm seems to be different at different stages (phase specificity). In the early development of the fertilized sea urchin or anuran egg, the gene action in the cytoplasm seems to be of little importance until the gastrula stage. At this stage, a more lively conversion of substances occurs in connection with an increased formation of enzymes and other specific proteins (27, 94, 161). An earlier period of lively nuclear control probably coincides with the development of the female germ cell in the ovary. Hadorn (162) points out that the effects of lethal genes in *Drosophila* cluster at phases of high developmental activity.

Hadorn and co-workers have added further interesting evidence about the development of lethal mutants of *Drosophila*; the work was reviewed by Hadorn (162). In the meander-lethal (*lme*) analyzed by Schmid (163) different organs were very differently affected. The body size was, for example reduced much more than the tracheal trunk, which therefore had a meandering arrangement. The effect of the *lme* gene resides in a deficient protein metabolism. Some step in the protein anabolism is probably blocked in the absence of the normal allele of *lme*. Imaginal discs and gonads showed normal capacity of development if transplanted into normal larvae. These organs were thus only secondarily affected by the lethal gene. However the eggs in the transplanted ovaries remained sterile.

In the lethal mutant *translucida* (*ltr*), arrest of development and death could occur in three different stages [see Hadorn (164)]. In those which attain the most advanced stage, a partial metamorphosis of head and thorax occurred, whereas the abdomen did not metamorphose. Also, in this case, certain primordia were only secondarily affected, as demonstrated by transplantation experiments.

The genetic basis of pathological development in mammals has been reviewed and discussed by Grüneberg (165, 166). Zwilling (167) explains the absence of wings and other defects in homozygous "wingless" chick embryos by a failure in the development of certain epithelial structures. From the effects of a homozygous lethal mutant gene (*Ki*) in mouse, Gluecksohn-Schönheimer (168) was able to infer that similar organizer phenomena and

inductive relationships exist here as in amphibia and birds. The homozygous *Ki* embryos which died at the age of 8 to 10 days after the fertilization presented abnormalities ranging from slight duplicity to more or less complete twinning.

Baltzer, Andres & Roth (169 to 173) transplanted different germinal regions of embryos of *Bombinator pachypus* into neurulae of *Triton alpestris*. Although the host tissue and transplant belonged to different orders, they showed normal inductive relationships and cooperated in the production of organs which could even show normal function. The species characters of the implants were, however, retained. Particularly the rate of development proved to be a property with pronounced species specificity. At a certain stage, however, a cytolysis and phagocytosis of the transplants occurred. The destruction of different organs took place in a definite sequence.

The experimental study of intersexes has been of outstanding value in approaching the question of the mechanism of sex determination. Seiler has published a comprehensive review (174) of the work carried out by himself and his co-workers on intersexuality in the highly dimorphic moth, *Solenobia triquetrella*. The intersexual individuals were earlier obtained by crossing tetraploid parthenogenetic females with males of a bisexual variety. It has now been shown that intersexual phenomena of a similar character can be obtained by crossing a female of the bisexual variety of *S. triquetrella* with a male of a different species, *S. fumosella* (175). In the latter case, the conditions are more closely parallel to those which prevailed in Goldschmidt's pioneer work on the gypsy-moth. In both the crosses mentioned above, an array of different steps of intersexuality was obtained. If an animal is intersexual with respect to one characteristic it shows the same average intersexuality also with respect to other characteristics. Seiler's interpretation is that the sex factors F and M in the *Solenobia* crosses are of about equal strength. Thus, neither of these can dominate and the determination of the sex is wholly left to variable phenotypic factors.

Goldschmidt (26, 176) found in *Drosophila melanogaster* that the dominant mutant, *Beaded*, in combination with one of the numerous *Minute* mutants gave male intersexuality of a degree varying according to the *Minute* used.

In work on axolotl, Humphrey (177) proved that a reversal of sex was possible also in females of the type *WW*. In contrast to the normal type *ZW*, it has no male factor (*Z*). The reversal was caused by the implantation of gonadal preprimordia of axolotl into embryos, 50 per cent of which belonged to the *WW*-type. The results demonstrated that the *Z*-factor is not essential for the development of the testis. The *Z*-factor may rather favor male sex differentiation by stimulating the development of the medullary (testicular) part of the indifferent gonad.

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PHYSIOLOGICAL EFFECTS OF HEAT AND COLD

BY RONALD GRANT

Department of Physiology, Stanford University, Stanford, California

The space allotted to this review has been devoted mainly to critical consideration of recent contributions that, in the opinion of the reviewer, are significant, controversial, and provocative of further investigation. For this reason, many important studies have been accorded only brief mention and minor aspects of some investigations have been discussed at some length. The review is thus an appraisal of the current status of certain aspects of thermophysiology, strongly colored by the opinions and interests of the reviewer. A complete coverage of the year's literature has not been attempted.

Introducing an article on "Regulation of Body Temperature" (the most significant postwar review of this field) Bazett (1) remarks that "research work carried out for war purposes contributed little to the basic physiology of thermal regulation in man." This remark could well be extended to the postwar period for, despite a formidable array of papers, very few of these can be said to contribute much to basic knowledge of the physiology of thermoregulation and its disturbances. Bazett's masterly exposition of the current status of thermal physiology in man may have done much to redirect research towards an attack on fundamental problems. His article and others in the absorbing series assembled by Newburgh have greatly simplified the task of the reviewer by providing a background for the discussion of more recent contributions and by making permissible the omission of many topics. In particular, discussion of technical and procedural problems has been avoided. To Newburgh's book, Hardy (2) contributes a concise summary of the physics of heat transfer and Yaglou (3) discusses methods of thermometry and calculation of indices of comfort. Methods for determining regional heat loss are reviewed by Day (4), and both the techniques and principles of the science of clothing are effectively summarized by outstanding authorities.

THERMOREGULATION

Central nervous system.—The most fundamental problem in thermoregulatory physiology is the nature of thermosensitivity itself, whether in peripheral sensory structures or in the "thermostats." That certain hypothalamic nuclei are sensitive to small changes in temperature has been confirmed once more by Folkow, Ström *et al.*, (5) using electrodes that could be utilized for either thermal conductive heating and cooling or diathermy. Blood flow changes in limb veins of cats were used as the chief criterion of effective stimulation and it was shown that hypothalamic warming caused greatly increased flow that was confined to cutaneous vessels and mainly to the foot pads (6). Results suggest that arteriovenous anastomoses are involved. Dilation was more pronounced and more easily elicited in fore than in hind

limbs and caused little change in arterial pressure. Small changes were demonstrated in the ear vessels but none in intestinal veins. Thus, this type of stimulus seems to evoke a pattern of vasomotion appropriate for promotion of heat loss. Curiously, no increase in flow through the tongue could be caused.

Ederstrom (7), studying blood flow by means of the photoelectric plethysmograph in dogs heated by radiation, came to the conclusion that the flow through the pads decreased although the temperature of the pads, which were not exposed to heat, increased and arteriovenous temperature differences indicated increased heat loss. The tongue also increased in temperature but flow increased about 100 per cent at 43° body temperature. A skeptical attitude towards these results seems appropriate until they can be confirmed by more direct methods. Ström (8) found hypothalamic warming to be much less effective if body temperature fell below normal; also, temperature change in the limb markedly influenced flow and the response to warming. When blood entering the limb was cooled, so that skin temperature fell to 31°, hypothalamic warming caused no vasodilation, although a normal response was seen in the limb receiving uncooled blood. Cooling by immersion had the same effect. When the immersed limb had been deafferented twelve days previously, changes in flow caused by changing the bath temperature alone persisted, but hypothalamic warming was much less effective. Unfortunately, these studies are not sufficiently detailed to be considered conclusive: if confirmed, they indicate an unexpected degree of "local sign" in the hypothalamus. Ström (6) notes the impossibility of deciding whether warming is excitatory or inhibitory to hypothalamic neurons but postulates that warming stimulates neurons that are inhibitory to the vasoconstrictor center. Dorsal root vasodilator fibers are not involved (9). Prolonged vasodilation followed a brief period of intense warming. Unlike Magoun *et al.*, Ström was unable to induce polypneic panting by hypothalamic warming although the areas stimulated (10) and the technique used were almost identical. Cooling of the hypothalamus did not cause vasoconstriction, although cooling of the anterior part while this same region was being warmed by diathermy reversed the vasodilation. Cooling the carotid blood did cause marked vasoconstriction but did not cool the hypothalamus, so the effect is attributed to stimulation of peripheral receptors in the head. The carotids are thought to supply little blood to the hypothalamus in cats. Hypothalamic temperature was found to be consistently about 1°C. lower than rectal. From jugular bulb temperatures Bazett (11) concludes that human hypothalamic temperature is usually higher than rectal.

The effects of electrical stimulation of the hypothalamus and of parts of the frontal lobes on cutaneous blood flow were also studied by Ström (12) in cats, using saw-tooth stimuli. When peripheral tone was high, stimulation had no effect but cessation of stimulation was followed by pronounced dilation, the intensity and duration of which were proportional to strength and duration of stimulus. With stimulation for ninety seconds, dilation began during stimulation but became more pronounced on cessation. If stimuli

were resumed during "post-stimulatory dilation" vasoconstriction occurred, as was the case with the initial stimulation if given at a time of low vasoconstrictor tone. Cutaneous vasomotor responses were obtained most easily from lateral preoptic and supraoptic regions but also from caudolateral parts of the hypothalamus where stimulation often caused more general vasomotor responses, respiratory changes, pupillary dilation, and somatic movements. Reactive points in the frontal lobe have similar effects and were found "medially in the white matter from the sulcus cruciatus converging caudally towards the supraoptic region." Changes in strength and frequency of stimulation often caused reversal of vasomotor effect, as in the experiments of Bronk, Pitts, and others. Stimulaneous warming and electrical stimulation of single hypothalamic sites gave, in general, the pattern of response to be expected from results of the individual stimuli, e.g., warming at a time of high vasoconstrictor tone caused vasodilation; electrical stimulation then caused vasoconstriction. Local cooling had no effect on the results of electrical stimulation. Strong electrical stimulation caused a poststimulatory dilation lasting 30 minutes, during which time hypothalamic heating or cooling had no effect. Barostatic vasomotor responses had little effect on cutaneous blood flow as measured, or on the responses to hypothalamic stimulation. After decortication, effects of hypothalamic stimulation were unchanged or accentuated, so it is concluded that they are not due to stimulation or corticohypothalamic fibers or circuits. Polypneic panting sometimes occurred with electrical stimulation of the hypothalamus, but this was usually accompanied by generalized sympathetic discharge and followed by a profound poststimulatory vasodilation. Like those of previous workers, Ström's experiments on electrical stimulation are hard to interpret and difficult to correlate with the results of thermal stimulation. The long persistence of poststimulatory effects suggests that the unidirectional stimuli used caused polarization or electrolytic damage: stimulation with alternating current might have been more illuminating.

Ström's technique seems to be a more sensitive method of detecting changes in thermoregulatory status induced by hypothalamic stimulation than methods used previously, although perhaps less satisfactory than modern plethysmographic techniques. But the nature of the peripheral changes induced, i.e., the meaning of "vasodilation" as measured by flow in superficial veins, remains to be determined. The absence of vasomotor responses to hypothalamic cooling is unexpected (they were observed by Hashimoto in rabbit ears). Possibly supplementary study of flow in deep veins might reveal such changes.

Temperature changes may act directly on hypothalamic neurons, increasing or decreasing their rate of spontaneous discharge. Support for this hypothesis can be found in the experiments of Bernhard & Granit, C. v. Euler, and others demonstrating that mammalian peripheral nerves show specific and differential thermosensitivity and can be caused to discharge repetitively by moderate thermal stimulation. Yet recent studies empha-

size the importance of peripheral sensory stimulation as an adjunct to central stimuli even in deep anesthesia and in species supposedly showing only "central" thermoregulation, such as the rabbit. Certainly there is no evidence that distinct central mechanisms are involved in "reflex" and "central" regulation. Existing data suggest the possibility that thermal changes may be effective through facilitation or inhibition of afferent nervous stimuli. It is usual to assume that sensory fibers affecting thermoregulatory centers are offshoots of those causing thermal sensations. However, it is certain that reflex thermal responses need not involve conscious recognition of temperature change and there is a good deal of suggestive, but inconclusive, evidence that purely thermal reflexes can be demonstrated in decerebrate or even spinal animals. Hensel (13) has discussed the phenomena of thermal sensation at some length, in connection with an elaborate study of the relation of thermal sensations to intracutaneous temperature under various conditions of internal and external thermal stimulation. The existence of true adaptation of thermal sensory mechanisms is considered proved. These authors and Maréchaux & Schafer (14) reject Weber's theory of thermal stimulation as entirely inadequate.

Probably even fragmentary understanding of the thermoregulatory functions of the hypothalamus will not be achieved until adequate techniques have been developed for the recording of brain stem potentials and until such methods have been applied to systematic exploration of the effects upon efferent discharge of hypothalamic neurons of peripheral and central thermal stimuli, as well as of the chemical agents supposedly acting on these centers. Progress in this direction has so far been negligible. The technically much simpler problem of defining the nature of the adequate stimulus for peripheral thermal receptors should be susceptible to attack with only slight modifications of the ingenious techniques now employed to analyze functions of other types of receptor. Action potential studies of the hypothalamus would obviously be inadequate unless the possible existence of slow potential changes (electrotonic "generator potentials") was investigated.

Electrical stimuli applied to several superficial and deep parts of the cerebrum cause vasomotor and respiratory changes (12, 15 to 19). The possible thermoregulatory significance of these areas is not yet clear but it seems probable that the cortex is involved in the more subtle aspects of thermoregulation, such as the upward thermostatic "reset" associated with exercise. Direct thermal stimuli have evidently not been applied to these areas experimentally. Teschan & Gellhorn (20) studied the effect of radiant heating of the exposed motor cortex in the anesthetized cat and concluded that heating above 45° causes excitation (disappearance of dial potentials and increase in frequency of the electrocorticogram). Those neurons most sensitive to electrical stimulation are most easily injured by heat, which is also more injurious to cells stimulated to convulsive discharge by picrotoxin (21). A surprising resistance to heat injury is indicated (e.g., 50°C. did not irreversibly destroy cortical sensitivity to electrical stimuli) if adequate precautions

were taken to prevent conductive heating of the thermocouple through the leads. Electrical excitability of the guinea pig cortex falls off rapidly below a rectal temperature of about 22° (22). Ten Cate *et al.* (23) found that the electroencephalogram of the curarized rat remains essentially the same between 39 and 32° rectal temperature, becomes reduced in amplitude below 30° and extinguished at 18 to 20°C. Above 39°, a general increase in amplitude of most electroencephalographic components occurred, with a decline in amplitude setting in above 41° and inactivity at 44 to 45°. There is nothing in these exploratory studies to suggest high thermal sensitivity in any part of the cortex.

A rapid fall of body temperature seen in rabbits subjected to light restraint was shown by Grant (24) to be due to activation of normal heat loss mechanisms and inhibition of shivering. Exposure to cold tends to inhibit the response. The effects of pyrogen injections are modified considerably. "Emotional" factors are blamed for the hypothermia which may be due to cortical modification of brain stem thermoregulatory function. Harris & de Groot (25) have described an emotional lymphopenia in rabbits which is abolished by lesions of the tuberalis and excited by electrical stimulation of the tuber or mammillary region.

Few advances have been made towards clarifying the functional connections between the hypothalamus and lower centers. Thompson & Bach (26) found that the arterial pressure, respiration, and knee jerk were affected in the same direction (enhanced or depressed) by stimulation of various posterior hypothalamic loci, and also by stimulation of or lesions in the bulboreticular facilitatory and inhibitory areas. Morin (27) has published a Marchi study of some hypothalamic connections in the guinea-pig: no physiological data were obtained. The gap between anatomical and physiological methods of studying the central nervous system is nowhere more regrettable than in relation to autonomic nuclei and their projections.

Some new data on shivering are discussed under HYPOTHERMIA.

Chemical disturbances of thermoregulation.—Agents that disturb heat regulation by a "central" action, such as bacterial pyrogens and many antipyretics, are usually supposed to act upon the hypothalamic thermostats to cause modification of their thresholds for thermal activation, but direct evidence for such actions is conspicuously lacking. Evidence regarding the site of action of pyrogens is discussed in the section on FEVER.

Several new antipyretics have been described and the mode of action of some antipyretics investigated (28, 29, 30) but in no case is there adequate evidence for a direct action on the thermoregulatory mechanisms. Chief interest in this field centers on magnesium. Heagy & Burton found that in dogs small amounts of magnesium salts injected intravenously suppress shivering in cold animals without causing vasodilation, and incite polypnea and vasodilation in warm animals. Hall & Ellis (31, 32) extended these results to rabbits and cats and showed that 2.5 mM per kg. of magnesium chloride injected intraperitoneally into rabbits depressed the cold-stimulated

increase in oxygen uptake although resting oxygen consumption was unaffected. These experiments are strong *prima facie* evidence that the magnesium ion at this concentration acts rather specifically on the central thermoregulatory mechanism, this action being conditioned strongly by body and environmental temperatures. Establishment of proof that these actions of magnesium are due to unitary action of the ion on thermoregulatory centers rather than to a complex of peripheral effects influencing the efficiency of thermoregulation, will require much ingenious experimentation, but no current experimental approach holds greater promise of contributing to solution of the enigma of thermosensitivity. Magnesium injections are well known to cause a sensation of warmth, usually attributed to vasodilation. The possibility that this may be due to direct chemical stimulation of thermal receptors should be explored, since proof of such an action would be strong evidence favoring a key function for magnesium in thermal reactions generally.

Anesthetics depress thermoregulatory reactions generally. The "cortical" anesthetics, urethane, alpha chloralose and chloralosane have been used widely in thermoregulation studies since they have minimal depressant effect. Grant & Robbins (33, 34) have shown that urethane injected intraperitoneally as a 20 per cent solution (the usual procedure) in cats and rabbits may cause cutaneous vasodilation, panting, and rapid fall in the body temperature. Since other hypertonic solutions (urea or glucose) given intraperitoneally act similarly, activation of the heat loss mechanisms under these conditions is attributable, not to urethane as such, but to hypertonicity of the solution in the peritoneal cavity.

Urethane given intragastrically or intravenously fails to cause vasodilation and it tends to inhibit panting. It causes prompt cessation of shivering and piloerection in animals exposed to cold. Thus, insofar as urethane has thermoregulatory effects, it depresses reactions. Nevertheless, its usefulness as an anesthetic (when intraperitoneal administration is avoided) for this type of investigation is shown by the fact that a rabbit so anesthetized can maintain a constant body temperature of about 36° at an environment of 2°C. by means of active shivering and piloerection. Further, it does not interfere with the vasoconstriction and suppression of panting occurring at the onset of fever evoked by pyrogen administration.

Regional differences in temperature.—The literature of the past year reveals a slow but satisfying penetration into the consciousness of physiologists of the fact that "core temperature," "deep body temperature," "average body temperature" and similar convenient abstractions have little direct physiological significance. The living body presents such a complex pattern of local areas of heat production and heat loss, variations in efficiency of convective heat transport, in specific heat etc., that even under the most favorable conditions any single temperature measurement can give only a rough indication of temperature in other parts. The assumption that changes in one "deep body" temperature reflect similar changes in other parts is permissible only under special conditions that are seldom met. Horvath's

(35) study of intravascular temperatures in the anesthetized dog emphasizes the steep gradients existing over short distances even inside vessels. Mead & Bonmarito (36) note the dependence of rectal temperature in man upon changes in the temperature of the posterior rectal wall due to proximity of the pelvic vessels, and therefore upon precise positioning of the thermocouple. Intragastric temperature is influenced strongly by the position of the thermocouple relative to the vena cava, liver, fluid contents and gas bubble, as well as by the vascular condition of the mucosa and probably gastric contractions (36). Appreciation of the many causes for variability of deep temperatures provides a ready explanation for many observations that have been regarded as "paradoxical," e.g., the sharp initial rise in rectal temperature usually seen when an animal is moved from a warm to a cold environment. Results described by Mead *et al.* (37) on subjects immersed to the waist in water show the bizarre nature of rectal temperature changes. Men who had been cooled by immersion in 10° water showed a sharp drop of about 1°C. in rectal temperature when bath temperature was quickly raised to about 43°. In some cases violent shivering occurred. In other cases profuse sweating of the upper body was seen when rectal temperature was minimal. Presumably the sudden fall in temperature was partly due to increase in venous return from the previously chilled legs, but the persistence of the fall for 30 minutes suggests that the rectal temperature observed during immersion was an artificially high "core" temperature. Obviously, with only rectal temperature to go by, interpretation of the effects on digital blood flow, sweating, shivering etc., in terms of central stimuli is virtually impossible. Bazett has repeatedly stressed the importance of temperature gradients developed along the long axis of the limb, also the importance of the routing of venous return, which affects rectal temperature especially (1, 11). The small range of skin temperatures measured on the trunk compared to those on distal parts depends not only upon differences in efficiency of vasomotor control but upon the impossibility of developing longitudinal gradients in the trunk. It is apparent that accurate measurement of changes in mean body temperature under varying experimental conditions is a major technical problem. Where such determinations are needed it would seem more practicable to measure rather changes in the heat content of the body. Development by Benzinger & Kitzinger (38, 39, 40) of a practical gradient calorimeter and "4 π " radiometer permits measurement of rapid changes in total heat loss and its fractionation. These instruments represent one of the major technical advances of recent years and should stimulate much fundamental research. Prouty & Lawton (41) have begun such investigations on animals.

In relation to thermoregulation, variations in body temperature are of importance only when they affect structures that are highly sensitive to change: there is no reason to believe that the body can recognize changes in heat content as such. Gross changes in temperature may affect heat balance by local effects, e.g., temperature changes in cutaneous vessels affect blood

flow markedly even after denervation (8, 42), but close control of temperature must depend on thermal stimulation of nonadapting peripheral thermoreceptors or central thermosensitive neurons. Evidence for the existence of peripheral thermal receptors capable of such action is lacking, moreover such receptors would be suitable only if situated deeply enough to be unaffected by surface gradients, hence this function is attributed to a single or dual "master" thermostat in the hypothalamus. This concept implies that the temperature of the hypothalamus is *the* temperature the body attempts to regulate. If this is so, variations in hypothalamic temperature should be small, and "paradoxical" activities of thermoregulatory mechanisms should be conspicuously absent when considered in relation to hypothalamic and surface temperatures. It is surprising that no serious attempt has been made to determine whether the activities of the thermoregulatory mechanisms correlate with slight changes in hypothalamic temperature in the near-perfect manner demanded by the current theory of an "absolute" thermostat. The literature of thermophysiology is choked with detailed studies the interpretation of which remains subject to doubt because rectal temperatures were used as a basis for predicting thermostat temperature without the necessary data required for making such a prediction. Recent conspicuous examples are Assmussen & Nielsen's work on the "resetting" of the thermostat in exercise and Robinson's (43) work on the relation of skin and body temperatures to stimulation of sweating.

It is perhaps not too much to hope that in future animal studies along these lines implantation of a thermocouple near the circle of Willis will be considered routine preparation. In human work, measurement at a suitable site or prediction of hypothalamic temperature from that of accessible sites is difficult. Bazett (11) has used the temperature of the jugular bulb to predict hypothalamic temperature, but it seems clear that slight changes in the temperature of the arterial inflow to the brain stem might be wiped out by the over-all effect of the brain mass, cooling in superficial sinuses, etc. Probably the best practical approach would be measurement of high aortic blood temperature. Eichna (44) found femoral arterial temperature to be consistently lower than rectal: this temperature may be close enough to high aortic to warrant its use, but this cannot be assumed.

Thermovascular responses.—The limitations of skin temperature measurements as an index of changes in blood flow have been recognized (37, 45) and adoption of plethysmographic techniques has led to marked improvement of publications in this field. An ingenious modification of the venous occlusion method (46), involving triggering of the occlusion by means of the electrocardiogram, permits instantaneous measurement of inflow and outflow rates in the vasodilated finger. During maximal thermal dilation, flow rates exceeding 140 cc. per 100 cc. per min. were recorded and both arterial and venous flows were found to be strongly pulsatile.

The existence of true reflex vasodilation in response to local cutaneous warming is still questioned (47, 48) but has been demonstrated effectively

by Kerslake & Cooper (49) who showed that radiant heating of the trunk or legs caused vasodilation in the hands within 10 to 15 sec., the response to heating the legs being unaffected by occlusive cuffs around the thighs inflated to 200 mm. Hg. Heating the trunk caused an early fall in rectal and oral temperatures. Delay in vasoconstriction when the radiant heating was turned off was not more than 6 sec. The main cause of negative results obtained by several investigators seems obvious: reflex vasodilation cannot be obtained when vasoconstrictor tone is high due to low central temperature. In the experiments of Goetz & Ames (47), the limbs were immersed for 10 min. in a 10° bath before testing. Floystrup & Skouby cooled the upper arms or neck (thereby causing peripheral vasoconstriction) to prevent warming of the hypothalamus on immersion of the hand in a 43° bath. Also, the test leg was enclosed in a cold space: this may have influenced its ability to respond to reflex vasodilator stimuli. The dilating effect of general body warming is not readily inhibited by local cold (50, 51) but reflex stimuli might be more readily inhibited.

Grayson (52) has shown that the effect of rising environmental temperature upon digital blood flow is complex. In subjects gradually warmed in a cabinet from 25° to 36°, the digital blood flow increased from 4 to 10 cc. per 100 cc. per min.; skin temperature showed parallel increase, rectal or oral temperature remained steady or declined slightly, and forearm blood flow was unchanged. Between 36° and 40°, digital flow and skin temperature decreased significantly and rectal temperature began to rise, the forearm flow again remaining unchanged. Above 40°, a secondary increase in digital flow raised the level to or above the previous maximum and at about 42° forearm blood flow began to increase. In two subjects studied, sweating began when body temperature began to rise and was preceded by vasoconstriction. Grayson concludes that the late vasoconstriction is mediated through sympathetic efferents and may have thermoregulatory significance, but he wisely avoids speculation regarding its mechanism of stimulation. The phenomena merit further study. The temporary decrease in digital flow may be due to barostatic reflexes brought on by venous pooling or other effects. It would be interesting to know whether this type of response is wiped out by heat acclimatization or by light exercise, also the point at which flow through arterio-venous anastomoses becomes prominent. As in many similar studies, it is not permissible to conclude that the early vasodilation is purely reflex, since hypothalamic temperature probably rose during this phase.

Local cold may cause constriction or "spasm" of peripheral vessels by a direct action not involving either true or antidromic reflexes (1, 11), although these effects are followed, in the warm subject, by dilation, possibly of inflammatory nature (11). Kramer & Schulze (53) have restudied the vasomotor effects of cold in some detail. Bader *et al.* (51) have noted that local vasodilation by cold is inhibited by general thermal vasoconstriction. Possibly a direct effect of warmth may aid dilation of peripheral veins during prolonged exposure to heat. Henry *et al.* (54) conclude that the tonus of leg veins is

decreased by warming, so that venous pooling is promoted: whether this effect is local or reflex was not determined. There is abundant evidence that maintenance of circulation in hands and feet exposed to cold is dependent mainly upon general heat balance of the body. This fact, long familiar to persons living in cold climates, is given scientific verification by Rapaport *et al.* (50) as is the familiar experience that foot temperatures fall sooner during general body cooling, and rise later during rewarming, than do hand temperatures. Similar conclusions can be drawn from a study by Mead *et al.* (37) on changes in digital flow in men exposed to rapid changes in environmental temperature. These experiments indicate that central temperature, rather than over-all skin temperature, is the main determinative factor involved in maintaining adequate digital circulation during local cold exposure. But in subjects showing marked vasoconstriction due to general cooling, local warming can cause a moderate increase in digital flow in the warmed member; also, in warm subjects suddenly exposed to cold, local cooling accelerates the rate of digital vasoconstriction and nonthermal vasoconstrictive stimuli (such as startle or deep breathing) have more effect on blood flow in a cooled hand than in a warmed one. These phenomena could depend upon a local sensitization to vasoconstrictive influences, but it is more likely that sensory influences from the cooled hand are capable of modifying the vasomotor influence of the hypothalamus, provided this is not above a critical temperature, this sensory influence having considerable "local sign."

Bader *et al.* (55) have attempted to determine whether individual differences in vascular responses to various tests can be utilized to predict cold tolerance, especially resistance to frostbite and ability to work for long periods with unprotected hands. Those individuals showing the more transient reductions in finger blood flow on immersion of the feet in ice water showed, with notable exceptions, the better general tolerance. Hursh (56) found the extent of cutaneous wheal following a "standardized" application of dry ice useless as a test of general sensitivity to cold. Young *et al.* (57) found that residents of the arctic showed greater peripheral heat loss than unacclimatized individuals. It seems probable that man has considerable ability to adapt to a cold environment by developing the capacity to maintain adequate peripheral circulation despite strong cold stress. Whether this is related to peripheral, central nervous, or metabolic "adaptation" remains to be clarified but the last is probably the major factor (58). Much might be learned from comparative study of the means whereby animals exposed to arctic environments avoid local cold injury while maintaining body temperature.

Skouby (59) found that patients with acrocyanosis fail to show peripheral vasodilation following tetraethylammonium bromide injections if the part is initially cool, and concludes that local hypersensitivity to cold is involved. Roth & Sheard (60) stress the obvious fact that the basal metabolic rate should be considered in evaluating the significance of cutaneous vasomotor responses: it is commonly ignored. Glaser (61) makes the interesting sug-

gestion that thermal balance may be established, in the same individual at different times, at markedly different temperature levels. Thus a man may sweat during rewarming at the same rectal temperature at which he shivered during cooling. These results (which are reflected in many other studies) may be due largely to inadequacy of rectal temperature data but suggest instability of thermal thresholds. Various aspects of thermoregulation may be affected differentially in this respect; thus Bader *et al.* (51) obtained profuse sweating in a rewarmed man some time before digital blood flow was restored.

The fate of blood shifted out of the skin has received little attention. Grayson (62) found that local heating of the abdominal wall near a colostomy caused a temperature fall in the latter, local cooling causing a corresponding warming. With general body warming, initial cooling of the gut was seen, followed by warming when body temperature began to rise. Glaser (63) found that generalized or local warming caused an increase in vital capacity, while cooling caused a decrease, suggesting that the lungs take up at least part of the blood diverted from the skin. Henschel *et al.* (64) confirm familiar experience in finding that skin temperature drops following a cold meal. Pellegrini & Riva (65) found that reflex changes in the temperature of the nasal mucosa on immersing the foot in 40° or 10° water are transient. Exposure to a hot environment while resting causes a 40 per cent decrease in renal plasma flow (66); exercise in the heat causes a further decrease, both exercise and heat causing efferent arteriolar constriction. Bader *et al.* (67) found that cold diuresis does not involve changes in renal hemodynamics but is due to decreased tubular reabsorption of water. It resembles water diuresis in most respects but differs in that chloride excretion is increased. Increased cellular hydration probably accounts for the diuresis.

Numerous studies on the influence of various physical therapy procedures on temperature and blood flow in deep tissues have appeared. Many of these contain material of much theoretical importance (68 to 73). The early optimism that very high frequency techniques might be a possible tool for achieving focal heating of deep sites such as the brain stem has not borne fruit in the form of fundamental studies.

Comparative data.—Rodbard *et al.* (74) claim that local warming of the turtle brain causes an increase, and cooling a decrease in arterial pressure. The effect is related to the "thermobaric" changes demonstrable in mammals and turtles subjected to general warming or cooling (75). The region giving maximal responses corresponds roughly to the mammalian diencephalon. No thermoregulatory significance is implied, but it is suggested that independent evolution of thermoregulatory ability in birds and mammals may have been based on a common, more primitive type of thermal sensitivity. Almost nothing is known regarding the means by which terrestrial poikilotherms are able to adapt physiologically to large shifts in body temperature. The possible existence of coordinating mechanisms such as are suggested by Rodbard's work merits precise study.

A thorough study of the relationship between body size and body temperature in homeotherms would probably contribute greatly to understanding of the limiting factors in thermoregulatory behavior. Rodbard (76) has assembled data illustrating the interesting fact that whereas the smaller mammals show a direct relationship between the logarithm of the body weight and body temperature, birds in the same size range show an inverse relationship. The larger mammals and large Ratite birds show, in general, an inverse relationship that extends the relation for small birds. Rodbard attributes the difference between small mammals and small birds to inability of the former to maintain high temperature because of poor insulation. This conclusion is based on misinformation (e.g., small mammals are said to be incapable of developing fever following pyrogen injections) and ignores the fact that it is only slightly more difficult to maintain a temperature of 104°F. than one of 98°, once established. The characteristically high temperatures of birds must be due to a difference in thermostatic "set" and remains intriguing. In general, thermostatic mechanisms of birds resemble those of mammals closely. Some apparent differences, e.g., the supposed insensitivity of birds to pyrogens, require confirmation. It is unfortunate that adequate data have not been assembled relating body size to temperature in a single species, e.g., the domesticated dog.

Theories of thermoregulation.—Hardy (77) has outlined an original concept of thermoregulation that demands critical attention. Thermal stress is considered divisible into "internal" stress (metabolic heat, pyrogens, antipyretics, etc.) acting directly upon the thermoregulatory centers and "external" or environmental stress, acting primarily through the cutaneous thermoreceptors. This classification of thermoregulatory stimuli is satisfactory, but the implication of "functional autonomy" of the two subsystems concerned seems unfortunate. Work published in recent years seems to the writer to emphasize the fundamental unity of all thermoregulatory phenomena. Changes in ambient temperature of the hypothalamus and afferent nervous stimuli of peripheral or central origin are distinct types of stimulus to the hypothalamic neurons, and the manner in which they are integrated remains a matter for conjecture, but the responses to both are channelled through the same efferent connections. Within a narrow range of brain temperatures, the centers appear to be highly responsive to sensory influence, so that the peripheral receptor mechanism acts as a "fine adjustment" on thermal exchange. With any marked departure from the normal range of brain temperatures, reflex thermoregulatory adjustments become more difficult to elicit. Whether or not the hypothalamus could continue to operate as a thermostat in the total absence of afferent influx is an intriguing question. In vigorous exercise, sweating and peripheral vasodilation are undoubtedly due mainly to increase of central temperature, perhaps aided by afferent stimuli of cerebral or deep somatic origin. What part cutaneous stimuli play in control of heat loss under these conditions is hard to determine. Robinson (43) found that men working at a constant rate showed

linear increase in rate of sweating with increase in skin temperature as the effective temperature of the environment was raised. Up to a skin temperature of 35.5°, the increase in sweating was achieved with negligible increase of rectal temperature, but above this level (approximately 32° effective temperature) rectal and skin temperatures rose about equally [cf. Grayson's (52) observations referred to above]. These data suggest that skin temperature is the chief factor involved in adjusting sweating rate to thermoregulatory needs up to the point at which rise of deep body temperature can no longer be prevented, but unfortunately one cannot rule out the possibility that hypothalamic temperature rose gradually over the range in which rectal temperature was stable. Certainly, some redistribution of thermal gradients must have taken place over this range of effective temperatures. That true reflex vasodilation and sweating can occur seems to have been proved beyond reasonable doubt by experiments on warming of the occluded arm. Rapid changes in cutaneous blood flow and sweating associated with sudden changes of environmental temperature are undoubtedly chiefly reflex, although it is questionable whether hypothalamic temperatures would show the "paradoxical" changes often reported for rectal measurements under these conditions. Yet such reflexes are wiped out or attenuated by significant changes in over-all body temperature. In the case of pyrogen injections, the rabbit seems to approach a purely "internal" stress response since the metabolic increase is independent of environmental temperature, and even of body temperature over a small range (78). But in man, the strength of shivering following pyrogens seems largely dependent upon skin temperature, suggesting that "external" stress plays at least an important secondary role in raising body temperature. "Emotional" hypothermia in rabbits (24) is inexplicable on the basis of current information. Sensitivity to central temperature changes seems to be wiped out or the threshold markedly changed temporarily, yet environmental cold can inhibit the phenomenon.

FEVER

Infectious fevers are usually attributed to "resetting" of the central nervous thermostats. Thermostasis is maintained less perfectly, but febrile animals are thought to oppose either a fall or a further rise in temperature. DuBois (79) has pointed out that in man fevers over 106°F. are rare. This applies also to fevers induced by bacterial pyrogens. In rabbits, high doses of pyrogen usually cause lower, but more persistent fevers than moderate doses and "staircasing" of fever above about 107°F. cannot be caused by repeated injections. Even when given to rabbits subjected to severe heat stress (with a rectal temperature of 106°), extreme hyperthermia is not induced although heat production is increased and transient inhibition of heat loss may occur (80).

Most of the phenomena of fever can be "explained" by the hypothesis of limited resetting of thermal thresholds and, lacking even fragmentary

information regarding the mode of action of the thermostats, it is exceedingly difficult to adduce crucial evidence either in support of, or in refutation of this hypothesis. But all or most of the data on fever can be explained equally well by postulating that pyrogens interfere with the motor mechanisms of thermoregulation. Chambers *et al.* (81) found that cats "decerebrated" anemically at the pontine or upper medullary level showed strong febrile reactions (including shivering and vasoconstriction) on injection of pyrogens and in some cases spontaneously. Since midbrain decerebrates never showed such reactions, the existence of a midbrain tegmental center that restrains the febrile response was suggested. This hypothetical center might be the "emergency regulatory mechanism" (79) that prevents fevers from reaching fatal levels, but surgical ablations have failed to demonstrate existence of auxiliary, high-threshold thermoregulatory centers. Unfortunately, Chambers' experiments cannot be accepted as proof that pyrogens can produce fever in the absence of the hypothalamus. Fever was spontaneous in many cases and defervescence was not demonstrated. Except in a single case, where anatomic transection at the pontine level is claimed, it cannot be assumed that the anemic hypothalamus was completely inactivated. The phenomena described demand more rigorous study, but suggest that the pontile animal can maintain a positive heat balance by both increased heat production and decreased heat loss. That such animals can shiver was shown by Dworkin.

There is clear evidence that pyrogens affect the lower brain stem directly. Profound disturbances of vasomotor control follow pyrogen injections in both the normal anesthetized cat and the midcollicular decerebrate (80). The many "side reactions" formerly attributed to toxic impurities in crude vaccines are produced also by purified pyrogens so that vomiting, defecation, urination, inhibition of gastric secretion (82, 83) and motility (84) are probably due to the action of pyrogens on medullary or lower central nervous centers. Chambers *et al.* obtained "side reactions" in anatomically decerebrated cats. Spinal animals showed reactions in pelvic viscera suggesting spinal cord stimulation. Spinal dogs showed leucopenia, but this may have been due to hypothalamic stimulation of endocrine secretions through the hypophysis. Windle *et al.* (85) describe profound cytological changes in endocrine glands produced by pyrogens.

Thus, pyrogens are potent pharmacodynamic agents whose action is by no means confined to thermoregulatory centers, nor is their action on heat regulation confined to production of fever, for in cats and rabbits exposed to severe cold they cause a delayed inhibition of shivering and consequent hypothermia (78). This effect is seen also with "pyrexin," derived from pleural exudate. A precise study of the effects of purified pyrogens on the semichronic decerebrate preparation is badly needed and an assessment of their possible effects on the bulbar facilitatory and inhibitory mechanisms would be valuable: possibly shivering is produced by an action at this point.

Ellis *et al.* (86) found that typhoid-paratyphoid vaccine does not affect the ventilatory response of rabbits to carbon dioxide.

The typical febrile response of rabbits to moderate doses of pyrogens consists of two phases of rising temperature separated by a phase of stable or declining temperature associated with activity of heat loss mechanisms (78, 87). Wylie & Todd (87) attribute the biphasic rise to the presence of two pyrogens, one mainly associated with the bacterial cells, the other with the medium of vaccines. Some vaccines cause a delayed fall in temperature below control levels, associated with toxic signs: this is attributed to the presence of a volatile (not heat labile) depressor substance. The evidence that these various effects are due to separable substances is far from convincing. Large doses of vaccines cause many-peaked fevers, the febrile reaction being characteristically cyclic. Development of tolerance due to repeated injections reduces the fever to a single peak, which may become delayed. Presence of more than one pyrogen in "purified" preparations is possible but the two-peaked fever is equally characteristic of fevers induced by pyrexin, which is a dried material but which induces a hypothermic phase in chilled rabbits even more strongly than bacterial pyrogens (78). Research with pyrogens is still hampered by doubt regarding the purity of these, despite the very high potencies obtained. Bacterial pyrogens are probably all polysaccharides but are not identical (88). Whether the small amounts of nitrogen and phosphorus remaining in purified pyrogens are essential is uncertain.

The fundamental nature of pyrogen action at the cellular or enzymatic level remains obscure. Peiss *et al.* (89, 90) found no difference in the cholinesterase activity of cerebral cortex homogenates prepared from febrile or normal rabbit brains, nor were the oxygen consumption or anerobic glycolysis rates of cortex slices different from normal in febrile animals. Patterson *et al.* (91) found no change in cerebral blood flow during the flush phase of fever induced by pyrogens, but a high correlation between flow and oxygen consumption that was not demonstrable in the afebrile subject. Hall *et al.* (92) found a significant depression of oxygen uptake in liver slices taken from rabbits at the onset of pyrogen fever: the significance of this is obscure.

Whether pyrogens act directly on the central nervous system also remains questionable, in view of the characteristic latency in onset of febrile reactions following intravenous injections. Bennett (93) found that rabbits infected with *Escherichia coli* did not develop tolerance to *coli* pyrogen, although repeated injections of this pyrogen induce a high degree of non specific tolerance to pyrogens either in normal or infected rabbits. It was therefore thought probable that the pyrogen is not the cause of fever accompanying infection. Bennett's studies are very clear cut. However, Neva & Morgan (94) found that patients recovering from typhoid or paratyphoid fever show greater resistance to the pyrogenic effects of somatic endotoxins of *Salmonella typhosa* or *Shigella dysenteriae* than do normal subjects or patients convalescent from other infections. Fever induced by inflammatory

exudate (pyrexin) is not associated with development of tolerance to subsequent injections of pyrexin or of pyrogens, nor does an animal rendered tolerant to pyrogens acquire tolerance to pyrexin (95). Thus, pyrexin might qualify as a "product of injury" responsible for fever induced by infection or by pyrogens, but there are many reasons for thinking that this is not so. The latency in development of fever following pyrexin injections is no less than that following pyrogens (78). Pyrexin does not appear in inflammatory pleural exudate (produced by turpentine) until the fever has subsided, about three days after injection (95). Lequire (96) found that suspension in homologous plasma prior to injection augmented the pyrogenic effect not only of vaccines but also of purified pyrogens. Plasma agglutinates bacterial suspensions and the blood of plasma-bacteria injected animals was found to retain pyrogenicity longer than that of saline-bacteria injected animals. But that purified pyrogens can be similarly held in the blood stream seems improbable. Unfortunately, no transfusion studies were made on rabbits given purified pyrogens and the experiments are not sufficiently extensive to be convincing. Influenza virus is pyrogenic in rabbits (97 to 100) but the nature of the reaction is entirely different from that due to pyrogens. The pyrogenic property is associated closely with hemagglutinating property and cannot be separated from the viral particles; it is relatively heat labile although infectivity for chick embryos can be destroyed by heat without abolishing the pyrogenicity. Neutralization with specific immune serum abolishes the pyrogenicity. The latency of pyrogenic response is longer than with bacterial pyrogens. Tolerance to pyrogenic effect is developed after a single injection, but no cross-tolerance to pyrogens is developed (98, 101).

Grant *et al.* have studied the possible participation of the adrenal and thyroid in development of fever induced by pyrogens (102, 103). Adrenalectomized rabbits, maintained healthy by desoxycorticosterone, respond to pyrogens in a manner indistinguishable from that of normal rabbits except that the increase in oxygen uptake (which is quantitatively no different) is associated with more prominent shivering, suggesting that shivering may replace epinephrine-stimulated calorogenesis. But a change in the mechanical characteristics of muscle contraction might account for the difference. Adrenalectomized rabbits show no loss of ability to develop refractoriness to pyrogens given daily or hourly (80). In thyroidectomized rabbits, which are usually slightly hypothermic, the initial response to pyrogens is as strong as in normals but the secondary temperature rise is absent or decreased and delayed. Shivering is pronounced and increased oxygen uptake plays a slightly greater rôle than in normal rabbits when the environment is cool. High environmental temperatures tend to restore the normal pattern of fever and thyroid medication restores it completely. The differences seen after thyroidectomy seem to be due mainly to depression of heat production, but there is probably some loss of reactivity to pyrogens.

In summary, it may be stated that our understanding of fever induced by pyrogens and viruses is extremely superficial. There is an unfortunate

lack of contact between investigators interested in bacterial polysaccharides for diverse reasons: distinct terminologies now in use impede such contact.

HYPOTHERMIA

Heart and circulation.—Among numerous exploratory studies of hypothermia, that of the Boston University group on 450 dogs cooled by immersion in water at 2° to 5°C. (the head, neck, and ventral thorax being unimmersed) is the most thorough yet available, especially with regard to cardiac dynamics (104, 105). Left ventricular pressures curves showed that the mean durations of systole and isometric relaxation were trebled as heart temperature fell from 37.5 to 24.2° and rate from 200 to 60 per min. Thus the "active" phase continues to occupy about 70 per cent of the cycle as in a tachysystolic heart. Despite sluggish cardiac activity, right atrial pressure remained normal and became elevated only when extrasystoles developed, causing gross irregularity. It is surprising, therefore, that the authors attribute the onset of decompensation to "accumulation of a metabolic debt" due to prolongation of the activity phase at the expense of diastole, coupled with a decreased rate of cardiac restitution, a fall in coronary pressure and an increased blood viscosity; also that cardiac irregularities and ectopic beats are regarded as a consequence of marked decompensation. The results of these and other authors indicate that disturbances of the conduction-excitation mechanism with ectopic pacemaker formation are the outstanding cardiac abnormality in hypothermia and the immediate cause of acute ischemia, sudden decompensation, and failure. Extrasystoles may be a consequence of "metabolic debt" but this cannot be established on existing evidence. For undetermined reasons, the heart is more apt to develop extrasystoles when cooled, whether locally or generally. In hypothermic man, atrial fibrillation develops regularly at about 29° and cardiac "failure" follows closely, presumably due to ventricular fibrillation in most cases. Hypothermia alone does not incite atrial fibrillation in dogs but may predispose to its incitement by excitatory agents (106). The vagi are not active at low temperatures, but direct depression of the conduction system may be a factor in permitting "escape" of ventricular pacemakers. Prec *et al.* (107) observed ventricular extrasystoles in pentobarbitalized dogs coupled with fibrillation in some cases, at 27° to 29°, but this was probably due to anoxia following respiratory depression by barbiturate since gross electrocardiographic abnormalities are dramatically reversed in such animals by artificial respiration (80). A study of changes in threshold of ventricular muscle during uncomplicated progressive hypothermia is badly needed.

Hoff & Stansfield (108) have developed a provocative hypothesis to explain establishment of tachysystolic pacemakers and fibrillation in the locally cooled heart. Currents of injury, reduced accommodation, and stair-casing of supernormality are thought to be involved in setting up the initial tachysystolic focus. Scherf *et al.* (109) have shown that establishment of one

tachysystolic focus provides the necessary background for the development of many.

It is unfortunate that no detailed analysis of electrocardiograms taken during cooling experiments has been made. Hegnauer & Penrod's analysis shows only that cardiac conduction, depolarization, and especially repolarization are impaired at low temperatures, the extent of the impairment increasing rapidly below 28°.

That the circulation remains adequate to supply the reduced metabolic needs of the body generally at low temperatures is shown by the fact that arterial and venous oxygen and carbon dioxide tensions remain essentially normal in dogs cooled below 20°. Postulation of coronary insufficiency therefore seems premature until coronary sinus catheterization data are available. Penrod (110) has made such measurements, but the results are not yet published. That cardiac anoxia due to failure of dissociation of oxyhemoglobin plays any important part in hypothermic arrhythmia and failure seems very unlikely in view of Hegnauer & Penrod's failure to find significant changes in gas content of arterial and mixed venous blood. Lange *et al.* (111) concluded that ST and T wave changes in hypothermic rabbits were due to shift of the dissociation curve since either acidification by acid phosphate or exposure to 8 atm. oxygen pressure reversed these changes. But the T wave changes seen were very slight and not necessarily due to anoxia, also it cannot be argued safely that the procedures used acted only by increasing the available oxygen. Lange evidently did not observe extrasystolic activity during hypothermia in rabbits: the published electrocardiograms show only sinus rhythm and it is implied that exitus occurred with progressive slowing of the heart ending in standstill.

Respiration and gas transport.—Meaningful data on the adequacy of respiratory support for tissue oxidations are obtained only when all aspects of respiratory function are studied simultaneously. Failure of external respiration is not a likely cause of hypothermic death except under anesthesia (104, 111, 112). Hegnauer & Penrod (104) have considered the influence of anesthesia, cold depression of the respiratory center, solubility of gases in plasma, shifts in the oxyhemoglobin dissociation curve due to cold and acidosis, hematocrit increase, and other factors on the adequacy of respiration in the hypothermic dog. Breathing persisted in some dogs at 18° brain temperature (11.8° rectal). Oxygen and carbon dioxide tensions of arterial blood remained essentially normal at 20° in most dogs. Venous blood gas analyses showed adequate dissociation and no stagnation in most cases. Acidosis, due to increased solubility of carbon dioxide, may offset to a considerable extent the decreased oxyhemoglobin dissociation at low temperatures. Breathing 100 per cent oxygen increased arterial and venous oxygen and carbon dioxide tensions and caused respiratory failure to occur at higher rectal temperatures. A remarkable finding was that blood gas analyses may continue to show adequate ventilation is taking place after all visible respiratory movements have ceased. Gosselin (112), using guinea pigs, noted re-

covery after 20 minutes of apnea. In anesthetized air-cooled dogs, Bigelow *et al.* (113) found that peripheral oxygen transfer and circulation were adequate down to 18°.

Metabolism.—It is generally stated that oxygen usage decreases "linearly" with body temperature, provided shivering is suppressed by anesthesia. The amount and persistence of shivering show striking individual variation, probably related to differences in depth of anesthesia, but in dogs shivering may persist at 20° brain temperature (104) and muscle rigidity at even lower temperatures. Oxygen consumption is maximal at about 28° (105). Possible endocrine effects on heat production have been ignored in acute hypothermia studies. Hegnauer & Penrod (104) found that in rats hyperthyroidism (thyroid feeding) or hypothyroidism (thiouracil) had no effect on survival rate following cooling to 15° to 16° in water. This result contrasts with the well established fact that thyroidectomized rats are less resistant to more gradual cooling (114). Lundholm (115) found no increase in blood lactic acid in rabbits exposed to cold air and concludes that epinephrine secretion plays no part in cold calorigenesis in this animal.

Penrod's (105) observations on shivering and oxygen consumption during rewarming of hypothermic dogs are of great interest. When rewarmed in air at 25° to 28° strong shivering occurred, beginning at a rectal temperature of 24° to 28°. When immersed in a 40° bath no shivering occurred, and air-warmed animals showed prompt cessation of shivering and decrease in oxygen consumption on immersion. These results suggest that shivering in dogs depends on peripheral sensory stimulation and is not excited by central cold alone. This does not exclude the possibility that central cooling facilitates peripherogenic stimuli. Unfortunately, no brain temperatures were recorded so it is possible that the bath raised brain temperature far above rectal. These results are in general agreement with most observations on the effects of direct cooling of the hypothalamus, which has usually failed to induce shivering. They are in sharp contrast to Sherrington's classical experiments on the chronic spinal dog which seemed to have proved that central cooling alone can excite shivering. Penrod's observations raise anew the possible alternative (or supplementary) interpretation of Sherrington's results, i.e., that return of cold blood to the head stimulated peripheral sensory receptors. Grant (80) found that rabbits anesthetized with urethane during exposure to 4°C. show prompt cessation of shivering which returns after rectal temperature has fallen several degrees. On removal to a 27° environment, shivering usually ceases within two minutes. On returning the animals to the cold room shivering recommences, sometimes within 15 seconds. These results suggest that shivering in the anesthetized rabbit is dependent upon peripheral stimulation but is conditioned by central temperature. Pilometer activity shows parallel changes. The problem of the "reflex" and "central" contributions to stimulation of shivering is, of course, merely a special case of the general problem of integration of peripheral and central stimuli in thermoregulation. It seems well to recall that Dworkin induced

"shivering" in rabbits with brain stem transections as far back as the calamus scriptorius, so that integrity of upper sensory mechanisms is not necessary for some cold-induced skeletal muscle activity.

Miscellaneous effects of cold.—Retarded bromsulfalein removal during hypothermia is attributed to decreased hepatic blood flow (116). In dogs, spontaneous movements, struggling and vocalization with some evidence of consciousness were seen at 20.5° and a knee jerk below 15° (104). There is little precise information on the effect of cold on the mammalian central nervous system and none that can be dissociated from indirect effects such as those due to anoxia.

Fasting pigeons exposed by Streicher *et al.* (117) to -40° survived up to six days with heat production increased about fourfold. Liver glycogen stores were depleted in eight hours, but blood glucose remained normal for at least 72 hours. Loss of weight at the time of death was 31 to 34 per cent. Under the same conditions, four domestic ducks survived 7 to 16 days, one that remained alive after 16 days having lost only 28 per cent of its body weight. While ability to maintain high levels of heat production undoubtedly plays an important part in this astonishing resistance of some birds to cold, the high efficiency of plumage as an insulating device must be the major factor involved.

It is generally agreed that acute hypothermia causes an increase in hematocrit and serum specific gravity. The physiological significance of these changes, so vigorously studied by Barbour, remains a matter of conjecture. Rodbard *et al.* (118), studying distribution of body water during hypothermia in rabbits and chicks found hematocrit and blood specific gravity moderately increased at 25° body temperature, but plasma and blood volumes (measured by T-1824) and thiocyanate space reduced 30 per cent. A comparable increase in these "spaces" was found in hyperthermia. These and other data make it apparent that dye methods, etc., fail to measure compartment volumes correctly under extreme conditions, considerable parts of the vascular and other spaces becoming inaccessible at times to injected dye. That true hemoconcentration occurs in hypothermia is certain. The theory that changes in the distribution of fluid associated with minor variations in body temperature have significant physical effect upon efficiency of heat transfer is now of historical importance only. That such changes may have important effects upon thermal thresholds is a more subtle possibility requiring further study.

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MUSCLE

By D. K. HILL¹

Postgraduate Medical School, University of London, London, England

This review covers the period from July 1948 to April 1950, but reference is made also to several papers which appeared earlier, and there are omissions towards the close of the period.

A rather arbitrary division has to be made between those aspects of the subject which are chosen for review and those excluded. The chemistry of muscle receives attention insofar as its connection with contractility is concerned. Thus it is appropriate to give space to the chemistry of the muscle proteins when the work concerned touches on the essential nature of the contractile process. On the other hand, no reference is made to work on the chemistry of muscle when it is connected with the metabolism rather than the contractility. No reference is made to the pharmacology of muscle, nor to the physiology and pharmacology of the nerve muscle junction, these being subjects which are reviewed elsewhere. It is customary to cover work dealing with certain pathological conditions, but it has been decided, in view of the limitations on space, to omit this section in the present review.

The lack of space has made necessary a choice between curtailing discussion of selected papers and foregoing any discussion of the majority. The latter was considered the better course, hence the very brief reference to a number of papers which are listed as a guide to further reading. It is not claimed that the coverage of the literature is complete, but omissions are, generally speaking, fortuitous rather than intentional.

The review is divided under the following headings: (a) muscle proteins, (b) biophysics, (c) the muscle membrane, and (d) miscellaneous. Under the first heading is considered the reaction of actomyosin and adenosinetriphosphate (ATP), ATP and the fibrous-globular transformation of actin, an analysis of the minute structure of the intact muscle fibre, electrophoretic analysis of muscle proteins, etc. Under the second heading are considered heat production and mechanical properties, theories of the mechanism of contraction, etc.

MUSCLE PROTEINS

The reaction of actomyosin and adenosinetriphosphate.—Two points have been advanced as being incompatible with Szent-Györgyi's view that the effect of adenosinetriphosphate (ATP) on actomyosin is the essential process in contraction. The first [Perry *et al.* (74)] is an assertion that the so-called "contraction" of actomyosin is simply a colloidal synaeresis due to a lateral association of particles: a muscle shortens but becomes thicker, while an actomyosin suspension simply shows an isodiametric shrinkage. The second objection is based on the observation that an actomyosin fibre shortens

¹ With the collaboration of A. V. Hill, University College, London, England.

under the influence of ATP only if it is unloaded; if it is under tension it lengthens instead [Buchthal *et al.* (14)]. Szent-Györgyi defends his position in respect of these two points (95). In the first place, the isodiametric shrinkage is ascribed to the random orientation of particles in an actomyosin gel: if they are oriented, as they can be, the actomyosin fibre behaves like muscle. Perry *et al.* (74) suggest that the synaeresis takes place by a lateral association of particles, but Szent-Györgyi argues that this cannot be so in view of the ability of an oriented fibre to shorten. As to the inability of the actomyosin fibre to develop tension, the explanation runs on these lines: ATP has two distinct functions; one is manifest in the action of ATP in lowering the viscosity of an actomyosin suspension by breaking down cross linkages between units [see also Mommaerts (68)]. The other function is to cause contraction, or coiling up of these units. In the living muscle fibre, the units are bound together by the accessory supporting tissue. Thus the units of an intact muscle cannot "flow" past one another, and the fibril is capable of developing tension when ATP is added [in this connection see Korey (61)]. In the artificial actomyosin fibril there is no relative restraint between units, and the assembly as a whole flows out if it is under tension.

Mommaerts (68) comments on this view of the dual effect of ATP on actomyosin. The viscosity of an actomyosin solution is reduced by ATP; this appears to be due to a dissociation of the actomyosin into its components. But dissociated actomyosin is not capable of contraction, so the disaggregation of an actomyosin suspension, referred to above as the suspected cause of the elongation of an actomyosin thread when it is loaded, cannot be assumed to be of the same nature. Although the connection of the "viscosity effect" of ATP on an actomyosin solution with the "contraction effect" is not plain, Mommaerts suggests that a study of the disaggregation in solution is useful. Some of the conclusions are as follows: (a) The effect is due to a combination with ATP, and hydrolysis occurs later at a rate which depends on the adenosinetriphosphatase activity of the solution in question. A reversal of the viscosity change accompanies the hydrolysis. (b) The initial combination is rapid. It apparently takes a "fraction of a second" to reach completion. (c) About 300,000 gm. myosin combine with 1 mole ATP. Mommaerts calculates that a single twitch involves a reaction of 1 mole high-energy phosphate with 200,000 gm. myosin. This near equality supports the idea that the viscosity reaction *in vitro* may have a connection, even though a rather obscure one, with the process of contraction in living muscle. In contrast with the reaction *in vitro*, the contraction of actomyosin fibres is not reversible; the same is true of intact muscle fibres when ATP is applied [Korey, (61)]. However, the reversal of the reaction *in vitro* is exceedingly slow compared with the relaxation of muscle.

Buchthal *et al.* (15, 16) have investigated the phosphorylation and adenine-nucleotide uptake of actomyosin and actin-free myosin, with a view to determining the nature of the chemical changes in the protein molecule which give rise to the observed physical effects when ATP and actomyo-

sin interact. The experiments were performed on threads of actomyosin or actin-free myosin, and the volume constriction (or synaeresis) served as a measure of physical changes. It was found that treatment with ATP results in a considerable increase in the amount of phosphate and nucleotide bound by both actomyosin and myosin. The changes are specific for ATP. It appears that the reaction involved is not directly related to adenosinetriphosphatase activity, since actomyosins with high or low enzymatic activity give approximately the same effects. A close correlation between volume change and chemical change in actomyosin is suggested by the specificity of ATP for both reactions. ATP causes phosphate and nucleotide uptake both in threads of actomyosin and actin-free myosin, whereas the constriction of volume occurs only in the presence of actin. It is concluded that the chemical changes must be located in the myosin moiety of the protein. Needham (70) has raised a problem which has to be considered if the close connection of ATP breakdown with energy provision for contraction is to be conceded. The optimal pH for adenosinetriphosphatase activity appears, from several accounts, to be much greater than that of the interior of a muscle fibre. The optimal is not lower than pH 7. The internal pH is likely to be in the neighbourhood of 5.9 [Boyle & Conway (12)]. But it has to be remembered that there is considerable evidence for localization of minerals in the fibre, so we cannot assume that the pH where the enzyme is acting is the same as the average internal pH.

A new method of studying the interaction of ATP with myosin and actomyosin by using monolayers of these proteins is reported by Munch-Petersen (69). The effect of ATP on a monolayer of myosin or actomyosin is to cause an expansion, and an expansion force can be recorded. The effect is greater with myosin than with actomyosin. The effect of ATP is specific, as ADP and other allied phosphates have no visible effect, except in much higher concentrations.

Borbiró & Szent-Györgyi (11) have shown that in the psoas of the rabbit the postmortem decomposition of ATP and the loss of contractility are parallel. This result is taken to support the view that the contractile matter of muscle is closely connected with ATP, although any substance of a labile nature is likely to show a decrease in a dying and degenerating muscle.

Ivanov (51) has studied the interaction of ATP with actomyosin. In agreement with other workers, he argues that the primary reaction of actomyosin gel to ATP is a synaeresis. It is reported that actomyosin fibres treated with ATP become more dense and opaque in the course of contraction. In a further paper (52), the same author has shown that the contraction of a muscle fibre following application of ATP is reversible by washing, but that an actomyosin fibre does not relax under similar treatment.

Schick & Hass (83) have described a method of isolating large numbers of mammalian skeletal and cardiac myofibrils in highly purified form without modifying their microscopic structure or their reactivity to ATP.

Szent-Györgyi (93) has amplified and extended his previous ideas in a

paper entitled "Free energy relations and contraction of actomyosin." In this paper, Szent-Györgyi's thermodynamical reasoning should apply only to a reversible chemical reaction: it may thus be criticized on the grounds that the shortening of actomyosin fibres following the addition of ATP shows no signs of reversal when the ATP is subsequently removed.

ATP and the fibrous-globular transformation of actin.—Straub & Feuer (92) have shown that globular actin contains ATP in a bound form. The hydrolysis of this ATP accompanies, and cannot take place without, polymerization of the actin molecules to give the fibrous form. Polymerized actin contains no bound ATP. It is suggested that here is a clue to the nature of the mechano-chemical coupling responsible for contraction. We have no proof that polymerization of actin occurs in contraction, but the authors state that "the outstanding properties of actin make it certainly suitable for such a role." They argue also, in view of Riseman & Kirkwood's (80) theory, that the polymerization of actin, accompanied by dephosphorylation of ATP, would "produce a drastic change in the electrostatic structure of the molecules of muscle fibres." Further work is in progress to test whether by doing mechanical work on fibrous actin it is possible to cause depolymerization and generate chemical energy in producing actin-bound ATP from ADP.

The electron microscope can be used to study the nature of the transformation of globular (*G*) to fibrous (*F*) actin [Rozsa *et al.* (81)]. Previous electron microscope investigations [Jakus & Hall (53); Astbury *et al.* (1)] have revealed the particles of fibrous actin as long, structureless threads. Rozsa *et al.* modified the procedure by allowing the *G*→*F* transformation to take place directly on the slide, and the film so deposited could be passed through the procedures required before photography, without any disturbance of the fibrous structure. The *F*-actin fibres prepared in this way are about 100 Å wide and appear to be made up of units or rodlets about 300 Å long. A conspicuous cross striation appears when two or more fibres aggregate to give a bundle. An ellipsoidal protein particle, having the dimensions of the rodlets seen in the electron micrographs (ca. 300 by 100 Å), would have a molecular weight of about 1.5×10^6 . This is much bigger than the molecule of globular actin, which is about 70,000. Thus, the rodlets themselves must be formed by polymerization.

While on the subject of the fibrous-globular transformation of actin, mention may be made of a theory of Szent-Györgyi's, recently propounded in a popular article (94). This suggests mechanisms by which ATP and actomyosin are together involved in excitation, contraction, and relaxation. In regard to excitation his picture is as follows. The actomyosin-ATP complex shows striking reactivity to the salt concentration: a change of 0.01 *M* at the appropriate concentration causes the reaction actomyosin-ATP \rightleftharpoons actin + myosin-ATP to take place. The ionic concentrations of intact muscle are such that the system is "balanced on a razor edge" and the two proteins just do not unite. The shift in ionic concentration, necessary for

their union and the contraction of the muscle, is brought about by the wave of excitation. As for relaxation, the suggested mechanism is equally simple. Actin remains in its polymerized state as a fibrous protein only in the presence of ATP. The ATP is split in contraction and the actin "falls into globules" which dissociate from the myosin-ATP: the muscle thus relaxes. This theory is at variance with the observations of Straub & Feuer (92), referred to above, which indicate that ATP hydrolysis accompanies polymerization of actin and not the reverse, as suggested by Szent-Györgyi. We are as far as ever from attaining unanimity in the problem of whether ATP breakdown is associated with contraction or with relaxation.

Analysis of the minute structure of the intact muscle fibre.—The axial periodicity of about 400 Å, the existence of which had previously been suspected by Hall, Jakus & Schmitt (33), has been described in more detail by Draper & Hodge (19, 20) who examined striated muscle of the toad with the electron microscope. This is regarded as a repeating pattern analogous to that observed in other fibrous proteins, such as collagen and keratin: there is no reason to suppose that it has any specific connection with the contractile function. It is found that there is a rough proportionality between the axial period and the sarcomere length in different states of contraction: this suggests that the elementary contractile unit is not longer than about 400 Å. By using high intensities of the electron beam it was possible to produce the effect of micro-incineration; this causes the disappearance of certain bands, due to the loss of volatile material. Other bands remain under this treatment. There is evidence that potassium salts are evaporated by such bombardment, but that calcium and magnesium salts are stable. Thus, suggestions are made as to the identity of the mineral substances in the various bands.

In addition to the 400 Å periodicity, Bennett (9) has described a zigzag structure which is interpreted as the image of a helical thread about 50 Å thick within the myofibril. About six turns can be counted within each 400 Å.

Pease & Baker (73) have put forward evidence which suggests that the myofibril is a tube-like structure. The wall of this tube contains the myosin filaments and also an "A-substance." The latter accounts for all of the recognized transverse bands of muscle except for the Z, M and N bands. The core of the myofibril is aqueous. It is claimed that the dense material, of which the Z, M and N bands are composed, appears to lie outside the myofibril in the interfibrillar space.

Schmitt (84) comments on the fact that an axial periodicity of 400 Å is found both by small-angle x-ray diffraction [Bear (8)] and by electron microscopy [Draper & Hodge (19, 20)], but points out that the situation is actually not so clear as it would seem to be. The largest meridional spacing observed in the x-ray pattern is about 27 Å, which is an order of the larger period. If the situation is similar to that of paramyosin [Bear (7); Hall, Jakus & Schmitt (32)], one might expect that the period observable as cross bands in the electron microscope would have a value of about 27 Å; the larger

period of 400 Å would be manifested as a geometric pattern of discontinuities within the bands. However, depending on the type of geometry of the intra-period structure, discontinuities at a spacing larger than 27 Å might conceivably appear. The solution of this problem will have to await a more detailed x-ray analysis and attainment of very considerably increased electron microscope resolution of the structure of the filaments.

Speidel (89) has examined the transverse arrangement of cross striations in myofibrils of striated muscle. The preparation consisted of an exceptionally favourable type of striated muscle from the pharynx region of the sea-spider *Anoplodactylus lentus*. A typical fibre is a short, slender, single-celled structure containing about a dozen coarse myofibrils. The sarcomeres are of large size. It was found that there was no helical shift of the striations as the fibre was rotated about its long axis: this particular point was examined in view of Szent-Györgyi's recent suggestion that actomyosin molecules are arranged in helical fashion within the myofibril.

Varga (96) and Rozsa *et al.* (81) have shown that under certain conditions fibrous actin may show striations.

Jones & Barer (58) have examined the fine structure of the sarcolemma of a muscle fibre with the electron microscope. No fibrous structure could be detected. Small spots are seen on the membrane: they are 0.04 to 0.1 μ in diameter and about 0.5 μ apart. The thickness of the dried sarcolemma is less than 0.1 μ.

Electrophoretic analysis of muscle proteins.—Dubuisson (21) has used an electrophoretic method of analysing the proteins of muscle and has investigated the changes produced by contraction and fatigue. The proteins in question include those which compose the contractile elements themselves. They are normally insoluble but can be extracted by solutions of high ionic strength. The extract from resting muscle shows two pronounced peaks on electrophoretic analysis: these are thought to be due to actomyosin and myosin. When the muscle is fatigued, the same peaks are seen, but extraction is more difficult: the reason for this decrease in extractability is not known, for it cannot be correlated with changes in ATP or with other alterations in chemical composition. When the muscle is frozen in the contracted state, as distinct from the fatigued state, the myosin and actomyosin are again much reduced in the extract. But now another protein appears in the extract: Dubuisson has named this "contractin." When muscle is allowed to relax after having been briefly tetanized, it yields the same extracts as normal muscle. The changes in extractability are therefore rapidly reversible and can only be observed if the mechanism is "fixed" in the state of activity. This result is significant, because the entire cycle of metabolic recovery takes a matter of minutes, and it seems, therefore, that this change in the condition of the proteins reflects some event connected with the contractile elements themselves, or with some chemical reaction which is rapidly reversed when the muscle relaxes. A similar deduction may be made from Dubuisson's observation that an extract of contracted or fatigued muscle added to a preparation of fresh muscle does not affect the solubility of the proteins.

Thus the soluble metabolic reactants are not responsible for the change: the effects observed must be connected with the protein molecules themselves or with smaller molecules closely bound to them.

If we assume that the phenomena reported are due to an increase or decrease in bond strength between protein molecules, one might well speculate on the possibility that the stiffening of the muscle substance which is known to take place in contraction is another manifestation of the same change in the proteins.

Dubuisson makes it clear that as yet it is not possible to decide whether the various changes in yield by extraction of the several protein fractions of muscle reflect solely the alterations in extractibility (although it seems fairly certain that this is an important factor) or whether the effects are partly due to changes in the total quantities present in muscle under the various conditions.

Spectral properties of myosin in the presence of ATP.—Ravikovich *et al.* (79) have shown that there is a change in the spectral properties of myosin as the result of addition of ATP and that the absorption spectra of mixed solutions of myosin and ATP are not obtainable by mere superposition of the individual curves. The intense band of myosin at 2775 Å is shifted to shorter wavelengths and approaches the band of ATP at 2600 Å. The appearance of a new band at 2640 Å is observed when ATP concentration is sufficiently high (0.5 mg. per ml.) and when myosin is of a sufficiently high enzymatic activity. Similar shifts are observed with actomyosin. The changes are reversible, and when the ATP is finally decomposed by the adenosinetriphosphatase the spectral absorption curve returns to its original form. The shift is specific for ATP. It is suggested that the ATP interacts with the tryptophane or tyrosine components of myosin, which are responsible for the main absorption band.

Rigor mortis.—Bate-Smith & Bendall (5) have made further observations in connection with the causes and the time course of development of rigor mortis. It was suggested earlier that violent activity immediately before death was the main reason for accelerated onset of rigor. The problem has now been more closely examined: two factors appear to be predominant (a) the pH of the muscle at the moment of death: this is determined by the amount of muscular activity immediately preceding death; (b) the magnitude of the glycogen reserve: the smaller the reserve the shorter the delay in the onset of rigor. This is consistent with the earlier report by the same authors that the onset of rigor coincides with the disappearance of ATP from the muscle. During the delay period, the breakdown of ATP is balanced by its resynthesis from the glycolytic cycle, but when the glycogen is exhausted the ATP level must fall.

BIOPHYSICS

Heat production and mechanical properties.—During the period under review, a series of papers on the heat production and mechanical properties of muscle has been published from Hill's laboratory (35 to 49). Attention has

been concentrated on the single twitch, as the irreducible unit of muscle activity. The energy (E) liberated in a twitch is described by an equation similar to that which holds good for a tetanus, viz.,

$$E = A + ax + \int P dx$$

where x is the amount of shortening, P the load, ax the heat of shortening, $\int P dx$ the mechanical work done, A the heat of activation and a a constant. The equation applies throughout contraction, not merely to total quantities. No energy is liberated in relaxation. The heat production begins very early (46) at about the middle of the mechanical latent period, as ordinarily observed, and starts off at its maximum rate: this is the activation heat. Three other effects become apparent at the same time, an increase of transparency [Hill (50)], an increased resistance to stretch (48), and the "latency relaxation."

The abrupt onset and the gradual disappearance of the active state of muscle have been followed by recording the resistance to stretch applied at various moments after a shock (42, 48). The full intensity in a twitch is as high as in a tetanus.

The question of whether relaxation is an active process has been examined by two methods (43): (a) the tension of a resting muscle is found to be measureable down to very short lengths; (b) the latent period does not vary with the initial length of the muscle. Both of these observations suggest the relaxation is not an active process, for otherwise the tension should drop to zero, and the latent period would be greatly prolonged by time occupied in shortening to take up slack.

Recent findings on the heat and work absorbed during a stretch have been briefly reported (45). It appears that the active state of muscle involves a physical framework which is reversibly coupled to chemical reactions. If the muscle is forcibly stretched while it is in the active state, a large part of the work done on it may be absorbed.

It has been shown (41, 42) that the onset of contraction is far too rapid to be accounted for by any substance diffusing inwards from the surface of the muscle fibre: an event, not a substance, must be propagated to the interior. A similar calculation (36) has given figures for the time lag which must be expected in detecting and measuring changes occurring inside a muscle fibre by means of a device, sensitive to one of the products capable of diffusing out, applied to the surface of the fibre.

The pressure changes which may occur inside a muscle during contraction have been measured (35). In a muscle such as the frog's gastrocnemius a pressure as high as 100 to 300 mm. Hg may be developed. This is the probable cause of the increased resistance to blood flow in leg muscles during strong contraction [Barcroft & Dornhorst (4)], and accounts for a substantial part, at least, of the reversible volume change accompanying contraction and relaxation.

"The dimensions of animals and their muscular dynamics" is the subject of an article by Hill (49). The known relation between speed of shortening and load is used to determine the power and efficiency of muscles under working conditions in animals of widely differing size. The limits of power development are considered in particular connection with the problem of propulsion in Cetacea (whales and dolphins). The general proposition is stated that animals of similar design should be able to move at about the same linear speed, or jump the same distance, whatever their dimensions.

The molecular mechanism of contraction.—From the physical point of view, muscle is an engine for the conversion of chemical energy into mechanical work, operating by means of reversible elastic stresses in the muscle proteins. In a system of this kind two types of cycle are possible, one involving changes in potential energy, and the other changes of entropy. Pryor (76) has discussed this matter, and concludes that the evidence appears to be in favour of an entropy cycle. One important difference between the two types is that in an entropy cycle the strength of intermolecular attractions should decrease during contraction, and in a potential energy cycle they ought to increase; observations on whole muscle suggest that they do in fact decrease [see also Weber (99) in connection with the effect of ATP in lowering the viscosity of protein solutions *in vitro*]. Pryor explains that the theory of a "chemical entropy engine" can be derived from a consideration of the properties of "imperfect rubbers," in which the strength of the intermolecular attractions is not negligible. A model of such a system is afforded by the contraction of tendon in a solution of mercury-potassium iodide: this solvent, or "plasticizer," has the effect of decreasing the intermolecular attractions by neutralizing polar groups; it may be washed out and the process reversed. Pryor suggests that a model of this sort should be capable of displaying a number of the thermal and mechanical properties of muscle described by Hill (34).

The electrostatic theory of contraction.—Edsall (22) in his contribution to a Discussion at the Royal Society on the subject of "Muscular Contraction and Relaxation; Their Physical and Chemical Basis," has drawn attention to a fact which is sometimes disregarded by many authors who have suggested analogies between the elastic properties of muscle and those of rubber: the structure of myosin differs from that of rubber in one important respect, namely in possessing numerous ionic and polar groups. It may be significant that the proportion of polar side-chain groups is higher in myosin than in any other protein yet analysed, except tropomyosin and the protamines. The concentration of these groups, expressed as chemical equivalents in the muscle fibril, is as high as that of the free ions. Large changes in the free energy of a protein molecule are produced by altering the ionic strength or dielectric constant of the surrounding medium and it seems likely that, whatever the driving mechanism of the contractile process, the electrostatic forces between the charged groups of myosin must vary appreciably as the protein chains fold or unfold. The theory of an electrostatic mechanism for

muscular contraction is not new [see Meyer (67); Weber (98)] and recently it has been revived by Riseman & Kirkwood (80), who suggest a charging of myosin by phosphorylation of the hydroxyl groups of serine and threonine residues by ATP. It is possible to account in this way for a change in the elastic modulus of muscle about equal to that occurring in contraction. Edsall lists the possible factors which might modify the electrostatic forces between the charged groups in the myosin molecule. These are: (a) binding or release of protons due to pH changes; (b) binding or release of other ions: e.g., phosphate ions; (c) variations of ionic strength of the medium; (d) variations of dielectric constant of the medium. The electrostatic theory faces at least one major difficulty. The extension of a protein chain by electrostatic repulsion requires the expenditure of free energy; it would certainly appear to be an active rather than a passive process. It would be hard to reconcile the theory with Hill's (38, 43) view of the relaxation as a passive process. As Edsall says:

It is, of course, possible that the net thermal effects are very small in relaxation, even though the free energy changes are large, but one cannot feel happy about such a conclusion unless it is possible to produce a mechanism that explains it.

Needham (70), although she admits that the matter is far from settled, favours the idea that relaxation is an active process and that ATP is broken down at that stage. The absence of heat production during relaxation is not considered as necessarily surprising, although a chemical reaction is in progress, for there is another example of this in the anaerobic recovery phase which goes on with very little heat production. In support of her view, Needham remarks on the well-known slowing up of relaxation in a muscle which is progressively fatigued by activity, suggesting that this would be characteristic of an active process.

The source of energy.—Fleckenstein & Hertel (25) have elaborated an earlier theory which attributes the energy of contraction to the exchange of part of the intracellular potassium ions with extracellular sodium. In a further paper, Fleckenstein (24) calculates that the osmotic energy of 1 gm. of frog muscle due to its selective permeability is about three times as large as the chemical energy which can be released by the ATP present in the same amount of muscle; the cation exchange accompanying the action current releases enough energy for the ensuing contraction. This conclusion does not bear careful scrutiny: it is based on what would seem to be an overestimate of the amount of ionic exchange which accompanies the action current itself, as distinct from any additional exchange which may occur later as the result of prolonged membrane changes or metabolic activity. As regards the changes accompanying the action current, we have no figures for a muscle fibre approaching in accuracy those which have been obtained for nerve, but there are indications that the ionic exchanges are of the same order of magnitude in the two cases. Thus, the energy changes associated with the action current are probably of the same order of magnitude as in

nerve: these are known to be extremely small compared with the energy released in a muscle twitch. On the basis of the osmotic theory it would follow that any work done by the muscle should be derived from the heat of the surroundings (as with the expansion of a gas). In other words, a muscle should cool when it does external work; in an isometric contraction there should be no change of temperature initially. The facts do not correspond with this hypothesis.

The excitation and contraction of the flight muscles of insects.—The beating of the wings of the higher orders of insects is produced by indirect muscles which are attached not directly to the wings, but span the box-like thoracic cavity. Pringle (75) has shown that these indirect muscles appear to be able to maintain the rhythmical oscillation necessary for flight without being under the influence of central control by the nervous system: that is to say, the oscillation of these muscles is self-perpetuating, the frequency being governed by the loading on the wing. Initiation of the rhythm is impossible unless the muscles have the normal nerve supply, but as soon as an impulse in a nerve fibre has once activated the muscle fibre, it contracts, and the tension developed then reactivates the fibre and the fibre oscillates. Pringle does not offer any suggestions as to the nature of the self-perpetuating mechanism.

Sotavalta (88) has made a detailed study of the wing-stroke frequency and of the flight-tone of insects. This comprises: (a) a determination of the frequency by acoustic and optical methods; (b) a study of the harmonic composition of the flight tone; (c) an analysis of the factors which cause variation of the frequency in one individual; (d) an examination of the differences in frequency as between different sizes and species of insect; (e) a discussion of the significance of the flight tone as a biological problem.

Other biophysical studies.—Wilkie (100) has studied the relation between force and velocity in human muscle, with elaborate control of all the factors involved. It appears that the equation describing the same relation for isolated muscle [Hill (34)] holds good also for the muscles of the human arm.

Knappeis (60) has investigated the influence of temperature on birefringence of the muscle fibre and actomyosin thread. In actomyosin threads the temperature dependence of the birefringence decreases with increasing stretch, corresponding to the reduced influence of thermal agitation at higher extension. In the muscle fibre the reverse is the case.

Buchthal & Kaiser (17) have investigated the mechanical performance of single muscle fibres, small bundles of fibres, and whole muscles. The optimum length for the greatest power output and for other specified activities has been determined.

Sten-Knudsen (90) has investigated the mechanical anisotropy of the isolated frog muscle fibre by determining the torsional elasticity and stiffness at various temperatures and tensions.

W. Josenhans (57) has used a modified Wöhlisch dynamometer, described by G. Josenhans (56), for the purpose of deducing a thermodynamical analy-

sis of muscle elasticity at zero tension. The object has been to distinguish between the two components of elasticity: (a) the thermokinetic, or "rubbery," component, and (b) the "cohesion" component due to a permanent cross binding between the elements. At zero tension the thermokinetic force is about 50 mg. per sq. mm. which is exactly compensated by the "cohesion" force. In contraction, the thermokinetic force increases above this value, and in maximal activity exceeds it by 100-fold.

THE MUSCLE MEMBRANE

Membrane potential and electrical signs of activity.—Liu *et al.* (65) have measured the electrical potential change accompanying development of rigor in iodoacetate-poisoned muscle. When secondary change resulting from the release of potassium is eliminated, the development of rigor is not accompanied by any depolarization: indeed, the primary event may even be an increase of polarization. If the potassium, which appears to be released by poisoning, is not washed away but allowed to accumulate, the muscle shows a course of depolarization which runs parallel to the development of rigor.

Ling & Gerard (63) and Ling & Woodbury (64) have studied the normal membrane potential of frog's sartorius fibres, its dependence upon metabolism, and the effects of stretch and changes of temperature.

Stoll (91) has studied the effects of electric stimulation of denervated muscle, and Fleisch & Waridel (26) have investigated the electric excitability of muscle degenerated due to nerve section.

Curtis (18), using microdissection methods, has found it possible to isolate small bundles of muscle fibres from the tortoise ventricle. Resting potentials as high as 10 mv. could be recorded. The conducted response causes the potential to fall to zero and remain there for as long as 3 sec. before suddenly repolarizing. Muscle tension continues to develop during the period of depolarization, and relaxation does not start until repolarization is practically complete.

Van Leeuwen (62) has made some observations of the afferent response from a nerve muscle preparation in the frog which contains a single muscle spindle.

Katz (59) has determined the electrical "constants" of the frog's muscle fibre membrane. This was done by the method previously used with single nerve fibres: it involves the application of rectangular current pulses and analysis of the resultant electrotonic potentials. In isolated groups of fibres, the transverse membrane resistance is 1,500 Ω per sq. cm. and in whole toe muscles it is 4,300 Ω per sq. cm. The membrane capacity is about 5 μ F per sq. cm. which is several times greater than that of a nerve fibre and this accounts for the relatively slower time scale of electro-physiological processes in muscle. It is incidentally shown that the falling phase of the end-plate potential is an electrotonic decay following the brief action of the neuromuscular transmitter.

MISCELLANEOUS

Gordon & Holbourn (28) have been able to record the sounds from single motor units in a contracting muscle of the human subject. The sounds heard by the subject himself during the contraction of muscles adjacent to the meatus may be resolved into sets of rhythmic clicks due to contraction of individual motor units. The various sounds heard during the contraction of a single unit of the *auricularis superior* have been recorded from a microphone inserted in the meatus; and the sounds of single units of the *orbicularis oculi*, by recording through the skin. The corresponding movements were recorded through the skin with a piezo-electric instrument. The movements or sounds are associated with action potentials which can be recorded simultaneously from the same motor unit. The movement lags behind the action potential by an interval of about 2 msec. In a further paper, Gordon & Holbourn (29) have extended the method for recording the contractions and action potentials of single units from the surface of exposed muscles in the cat, the activity being initiated reflexly. Comparison of the results for different parts of the same muscle (*tibialis anterior*) shows that this muscle contains a mixture of quick and slow fibres: it is thought that this is also the case for other muscles, but there is difficulty in making a fuller investigation because the mechanical records can only be made from the most superficial motor units.

Barcroft & Dornhorst (4), using a plethysmographic method, have been able to show that the pressure in the blood vessels due to rhythmic contraction of the gastrocnemius-soleus muscle of the human subject produces a mechanical resistance to blood flow. During an exercise in which the subject pressed a weighted pedal once a second, the blood flow was reduced to 40 per cent of what it would otherwise have been. This confirms what had been previously suggested, namely, that the effect in man would be similar to that in a dog's muscle, and the less direct evidence of Hill (35) in connection with the pressure developed in the gastrocnemius of a frog had pointed to the same conclusion.

Brown & Burns (13), in a paper entitled "Fatigue and neuromuscular block in mammalian skeletal muscle," have described experiments designed to obtain some quantitative estimate of the importance of neuromuscular block in reducing the tetanic tension of a fatigued muscle. It was found that block starts to develop before there is any decline in tetanic tension, and that when the latter does appear it is not due to the blockage of transmission. This surprising result is thought to be accounted for by the increased tension-time (the area under the isometric tension-time curve) which a fibre appears to be able to develop after it has been rested by block: this seems to be sufficient to compensate almost exactly for the loss of tension due to its failure to respond to every nerve impulse.

Singh & Singh (86, 87) have reported on experiments in connection with the tonus of unstriated muscle and they claim to have demonstrated that in this type of muscle relaxation is an active process.

Gualtierotti & Milla (31) have shown that there is a tendency to synchronization in different motor units of a muscle. The gastrocnemius of an anaesthetised or decerebrate dog was stimulated reflexly. Action potentials were recorded by a needle electrode. The frequency of the potentials was either 6 or 12 per sec. It was deduced that two asynchronously-oscillating potentials tended to synchronize.

Arienti (2) has made an oscillographic analysis of human walk, and (3) an electromyographic study of human locomotion. Fessard & Paillard (23) and Paillard (72) have studied the simultaneity of execution of voluntary movements. Bauwens (6) has given an account of the physiological principles underlying the use of electromyography and a description of the types of records obtained in various conditions. Jasper & Ballem (55) have described experiments in which they recorded unipolar electrograms of normal and denervated human muscle. Garb & Chenoweth (27) have recorded electrograms of the isolated papillary muscle of the cat's heart. Mention must be included of papers by Ralston & Polissar (77) on the dynamic features of human isolated voluntary muscle in isometric and free contractions; by Simonson *et al.* (85) describing the measurement of the elastic properties of skeletal muscles in situ; by Newman (71) describing a new device (the "myometer") for measuring muscle strength; by Rashevsky (78) on the locomotion of animals; by Granit & Suurosoet (30) on the subject of self-regulation of the muscle contraction by facilitation and inhibition from its proprioceptors; by Loofbourrow & Gellhorn (66) on "Proprioceptively induced reflex patterns"; by Saunders (82) on the metabolic cost of passive cycling movements; by Jalavisto *et al.* (54) entitled "An increase in the blood flow through muscle following rhythmical activity"; by Walker (97) showing that there is potentiation of twitch tension and prolongation of action potential induced by reduction of temperature in rat and frog muscle. Benoit (10) has described a transitory rapid rhythmic response of striped muscle.

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DIGESTIVE SYSTEM¹

BY E. S. NASSET

Department of Physiology and Vital Economics, University of Rochester School of Medicine and Dentistry, Rochester, New York

THIRST, APPETITE, AND HUNGER

Wolf (1) presented evidence, from experiments on the dog and man, that the thirst threshold may be largely determined by the severity of cellular dehydration. The decrement in cellular water at the thirst threshold is computed to be 2.15 ± 0.64 per cent in the dog and 1.23 ± 0.48 per cent in man. Additional evidence for the importance of gastric distention in the regulation of drinking was presented by Towbin (2). A dog with esophagostomy sham drinks 250 per cent of his water deficit before temporary satiation occurs. Distention of the stomach during sham drinking, either with water or a water-filled balloon, results in essentially normal drinking. Section of the vagi abolishes the effect of gastric distention on sham drinking. According to Archdeacon, Presnell & Walton (3) the administration of either atropine or pilocarpine has little or no effect on the 24-hour intake of water; atropine depresses temporarily both food and water intake.

Janowitz & Grossman (4) presented the interesting fact that dogs and rats fail immediately to eat increased quantities of a diet that is diluted with cellulose. These animals tend to continue eating a fixed volume of food and only make slow and imperfect compensation for calorie deficits. The influence of prefeeding on the quantity of food ingested was investigated by Janowitz & Grossman (5). A portion of the daily ration placed in the dog's stomach, 20 min. prior to the usual feeding time, either by mouth or gastrostomy, results in a corresponding reduction of the quantity of food voluntarily ingested. Food introduced by gastrostomy 4 hr. before the usual feeding fails to alter the normal intake. Janowitz & Grossman (6) failed to find any correlation between hunger sensation and the thresholds for salt and sweet taste.

MOUTH

The functions of the parotid gland were reviewed by Nash & Morrison (7). A method for the chemical determination of citric acid in saliva was developed by Zipkin & McClure and applied in a study of dental erosion (8). The chemical work appears to be very well controlled, but there is some question as to the validity of the correlation claimed to exist between citric acid concentration of saliva and the severity of dental erosion. The severity of erosion is expressed by the index numbers 0, 1, 2, and 3, which indicate absence of erosion, mild, moderate, and severe erosion, respectively. Unless the index numbers 2 and 3 represent precisely twice and three times the

¹ This review covers the period from approximately June, 1949 to June, 1950.

erosion represented by index number 1, the averages derived therefrom have at best an indefinite meaning. This is not to deny a possible relationship between the two items compared, but it seems likely that its numerical value may require revision.

A water-soluble, nondialyzable fraction of saliva was prepared by Hill *et al.* (9). It is bacteriostatic for *Lactobacillus acidophilus* and on injection in the rat the glucose tolerance curve is elevated and prolonged.

It is interesting to note a renewed interest in the physiology of mastication. Howell *et al.* (10) devised an electronic strain gauge for the measurement of oral forces. Maximum biting forces in four human subjects ranged from 11 to 25 kg. for the incisors and from 29 to 90 kg. for the molars. The occlusal contact area effective in mastication was determined by Yurkstas & Manly (11). Wax impressions of the bite were transilluminated and the occlusal area estimated from the amount of light transmitted to a photoelectric cell. The areas measured by this method are only 1/6 to 1/10 as great as those of other workers.

STOMACH

Secretion of inorganic components.—Further work on the electromotive forces present in the resting and active stomach led Rehm (12) to reconsider his earlier position that these forces are adequate to account for the osmotic work of acid production. He now suggests that most of the free energy involved may be supplied by some unspecified redox system and that the energy derivable from electromotive forces may assist in driving the reaction in the normal direction. The sites of electromotive force production and the course of inward and outward flow of current are not specified.

On the assumption that gastric juice is a mixture of two components of constant, isosmotic composition, Fisher & Hunt (13) derived a mathematical expression relating volume of juice to the amounts of acid and neutral chloride. Application of this expression to the data of others gives the following values: parietal secretion contains 160 meq. of hydrogen ion and 10 meq. of neutral chloride per l.; non-parietal secretion contains 125 meq. of neutral chloride and 45 meq. of bicarbonate per l. The composition of parietal secretion remains constant for both histamine and insulin stimuli. An interpretation of the data of others led Hunt (14) to state that the difference between duodenal ulcer hypersecretion and normal secretion of gastric juice is the result of peripheral rather than central hypersensitivity.

Davenport & Jones (15) reported further work in a systematic study of the metabolism of the mouse stomach. The pyruvate turnover is 2 to 4 micromoles in a period of two hours which is considered grossly inadequate to account for the 18 micromoles of inorganic acid produced in the same time. Terner (16) concluded that back-diffusion of hydrogen ion occurs in the amphibian gastric mucosa *in vitro*.

An attempt was made to determine the parietal cell "secretion pressure" by Roback, Grossman & Ivy (17). In acute experiments on the dog, the pro-

duction of acid in response to histamine stimulation ceased when intragastric pressure was raised to 25 to 30 mm. of mercury. They concluded that cessation of secretion was due to collapse of the capillaries. Davies & Turner (18) attempted to solve the same problem by using flaps of amphibian mucosa *in vitro*. They found that secretion of acid occurs against an applied pressure of 120 mm. of Brodie solution, which is only about one third of the maximum pressures used by Roback *et al.* to suppress secretion in the dog. Within plus or minus 50 mm. of Brodie solution pressure, the secretion of acid in the isolated amphibian mucosa is independent of the magnitude and direction of the applied pressure.

Dragstedt *et al.* (19) reported new evidence for the importance of the antrum in gastric secretion. The 24 hr. secretion of Pavlov pouches is reduced as much as 75 per cent by making a fistula of the antrum that drains to the outside. Whole stomach pouches with the vagi divided are made to increase their 24 hr. secretion several fold when the antrum is removed from the stomach and made into a diverticulum of the duodenum. Both Pavlov and whole stomach pouches respond in the same way when the antrum is made into a diverticulum of the transverse colon. These investigators conclude that the antrum is an organ of internal secretion. It would be informative to irrigate the antral fistula with chyme and other solutions and also to try simple distention. The work of Glass & Wolf (20) on human subjects lends further support to the idea that the pyloric region of the stomach is involved in the production of hydrochloric acid. The normal gastric response to intravenous insulin is an increase in hydrochloric acid, pepsin, and mucin. The peak for hydrochloric acid secretion occurs approximately 20 min. later than the peak for pepsin and mucin. In patients who previously had been partially gastrectomized the hydrochloric acid response was much diminished or absent, but the pepsin and mucin response was normal. It was concluded that the vagi directly affect the cells which produce the organic components, but probably affect the parietal cells indirectly by means of gastrin produced in the pyloric mucosa.

Hellebrandt & Houtz (21) report that the ingestion of the natural carbonated saline waters increases acid secretion and gastric motility. From older work and the recent work of Hale & Ivy (22) it is known that distilled water is also an effective stimulus for gastric acid production.

Goldsmith *et al.* (23) studied the iodine concentration in 10 human tissues 3 to 159 hr. after the intravenous administration of radioactive iodine. The gastric tissue concentration of iodine was always more than twice that of serum. The results of two investigations [Mason & Bloch (24) and Lagergr  n (25)] indicate that secretion of gastric acid is not necessary for the gastric secretion of iodide; hence it is not a component of the parietal cell secretion.

Secretion of organic components.—Glass (26) reviewed his own work on the origin and function of gastric mucin and some of the factors that control its secretion. Komarov *et al.* (27) concluded that the increased secretion of

"dissolved mucin" from a gastric fistula in response to sham feeding did not run parallel with the secretion of acid and pepsin. They suggest, therefore, that the respective secretory cells respond selectively to sham feeding. It may be well to emphasize here that the methods are not as accurate for pepsin and mucin as they are for acid. Glass *et al.* (28) reported that lysozyme has no effect on either gastric or colonic mucus *in vitro*.

The work of Fox (29) suggests the presence, in normal human gastric juice, of a nonpepsin proteolytic enzyme. Patients with a sprue relapse do not secrete this material. A connection with Castle's intrinsic factor is suggested. The enzyme determinations might have been more convincing had boiled juice been used in the blanks. According to Ternberg & Eakin (30), normal gastric juice and hog gastric mucosa contain apoerythein, a substance capable of combining with vitamin B₁₂. This material also is suggested as being related to Castle's intrinsic factor.

Milhorat *et al.* (31, 32) reported a material obtained by fractionation of gastric mucin and gastric mucosa which may be α -tocopheryl-*p*-hydroquinone. Both gastric material and the synthetic compound reduce the creatinuria of patients with progressive muscular dystrophy.

The gastric acid-phosphatase activity was determined by Changus & Dunlap (33) in patients with carcinoma of the stomach. Twenty-four of 25 patients produced more than 10 units of enzyme per 100 ml. of juice; nine of ten normal controls produced less than this amount. Komarov *et al.* (34) found that very little neutral red is excreted in the stomach. Ashford *et al.* (35) suggest that the human being differs from most laboratory animals in the pepsin response to histamine stimulation. They claim that the total output of pepsin runs parallel to the production of hydrochloric acid.

Secretion inhibitors.—The assay, and hence the fractionation, of gastric inhibitors has been much retarded in the past because a quantitative measure of gastric secretory inhibition was not available. Code *et al.* (36) and Blickenstaff & Grossman (37) described methods that show considerable promise. The first of these seems preferable because the maximal response to histamine of each animal is determined before a test is made. For purposes of assaying a gastric inhibitor, the test animal is given just enough histamine to bring about a response which is 50 to 60 per cent of the maximal; when this is established, the inhibitor is administered and the percentage reduction in response observed. The second method (37) involves the use of a fixed dosage of histamine regardless of the responsiveness of the individual animal. The latter method was used to test the effect of two pyrogens on the secretion of hydrochloric acid. No inhibition occurred without pyrexia, but there was a delay of approximately one hour after the onset of pyrexia before inhibition of secretion was apparent. It was concluded that pyrexia is not directly connected with the inhibition.

Gambill *et al.* (38) studied the efficacy of orally administered enterogastrone preparations. Forty-eight patients with duodenal ulcer were studied; some received enterogastrone and the remainder were given placebos.

Neither the patients nor the physicians who made the periodic examinations knew which subjects were receiving the active and which the placebo medication. Thirty-nine patients completed a year of treatment. Of the 22 who had received enterogastrone 77 per cent showed clinical improvement; of the 17 who received the placebo 59 per cent showed a comparable improvement. The investigators concluded that the slight apparent advantage of enterogastrone is too small to be conclusive.

Blackburn *et al.* (39) described a gastric secretory depressant which is precipitated from gastric juice in 80 per cent alcohol. It was found in relatively large amounts in the achlorhydric gastric juice of five pernicious anemia patients; it was absent or present in small amounts in normal acid gastric juice. With the aid of certain "group reagents," Wick *et al.* (40) arrived at the conclusion that the antiulcer activity of urogastrone preparations is associated with a polysaccharide. The Shay rat was used for assay of their preparations. In general, this type of animal preparation is unreliable for this purpose; the extent and intensity of ulceration cannot be expressed in quantitative terms and hence the results obtained are often misleading. Huff *et al.* (41) suggest that urogastrone is a glycoprotein which may be an end product of the metabolism of the pituitary gonadotrophins. They point out that the diminished incidence of ulcer during pregnancy may be due to an increased production of urogastrone from the metabolism of chorionic gonadotrophins.

Miscellaneous.—Avey *et al.* (42) studied the effect of atropine on the interdigestive phase of gastric secretion in normals and in peptic ulcer patients. The drug exerted the usual effect on gastric secretion, but the percentage reduction was greater in the normal individuals. Weinstein *et al.* (43) made a study of the insulin test in 125 patients before and after vagotomy. Some of these patients were also subjected to gastroenterostomy or subtotal gastric resection. The simplest situation is represented by a group of 20 patients who were vagotomized for uncomplicated ulcer. Eight of this group of 20 gave a positive insulin test and 12 were negative. The ulcers healed in 75 per cent of the cases in both negative and positive groups. Little correlation is evident between the postvagotomy insulin test and the clinical improvement subsequent to operation. Jamieson (44) states that an isolated gastric pouch in the human did not respond to feeding, histamine, or insulin.

Subsequent to 42 post mortem examinations of the dog, Hilsabeck and Hill (45) published a description of the anatomy of the vagus and a technique for its interruption. Inberg (46) stated that, in the cat, nerves other than vagi and splanchnics are concerned in afferent impulses from the stomach.

Babkin (47), in what possibly is his last paper, reports explorations of the cerebral cortex for centers which affect the stomach. He found only two, namely, the orbital surface and the anterior end of the cingulate gyrus. Electrical stimulation of these areas usually resulted in motor inhibition of the antrum. The impulses are evidently relayed through the gastric vagal centers because they are interrupted by vagus section. Thus, the cerebral centers seem to moderate vagal activity which is motor for both gastric

secretion and motility. If cerebral control is diminished or abolished gastric activity is augmented and the possibility of ulcer development is enhanced.

Jefferson *et al.* (48) tried unsuccessfully to produce the postgastrectomy and postvagotomy syndrome in dogs. Cordier & Chanel (49) state that reducing the oxygen of inspired air to 12 per cent has no effect on gastric evacuation of 5.4 per cent glucose solution. Wirts & Rehfuß (50) report that an ion exchange resin reduces gastric acidity without a subsequent rebound. Segal *et al.* (51) devised an ingenious compound for determining the presence or absence of gastric acid without intubation. An ion exchange resin is combined with quinine and in the presence of gastric acid some of the quininium ion is exchanged, absorbed, and promptly excreted in the urine. Thirty-four of 38 subjects known to secrete free acid excreted quinine in the first, second, and third hours after ingesting the resin. Twenty-five subjects with known achlorhydria failed to excrete quinine in the first hour. With some refinements this method may yield quantitative information on the secretion of free gastric acid.

Three antihistamine compounds were found by Ashford *et al.* (52) to be without effect on the gastric response to histamine stimulation. Longino *et al.* (53) found that a quaternary amine was much more effective than atropine in depressing gastric secretion and motility. Katz *et al.* (54) claim a lower "pathology index" for Shay rats treated with acetylsalicylic acid. Hunt (55) reported that the human stomach absorbs 1.5 per cent of ingested water from volumes of 500 to 800 ml. The data seem scattered and inconclusive. By means of biopsy specimens taken from the human stomach, Wood *et al.* (56) correlated morphology of the mucosa with secretory activity.

ULCER

Neches (57) reviewed several theories concerning the origin of acute peptic ulcer. His opinion is that temporary devitalization of the mucosa is a prerequisite for the development of ulcer. The importance of acid and pepsin in the etiology of acute ulcer is discounted.

A consideration of six cases of peptic ulcer in monozygous twins suggested to Ivy & Flood (58) that organ susceptibility to ulcer may be inherited. A plea is made for others to seek and report similar data. Doll *et al.* (59) reviewed the medical histories of 100 medical students who, 15 years earlier, had been the subjects of histamine tests. The individuals who secreted 100 ml. of gastric juice or more per hour were the ones who later developed dyspeptic and ulcer symptoms. Platt *et al.* (60) report a difference in the glucose tolerance of ulcer patients as compared with normal controls. Whether the sugar is given orally or intravenously the blood glucose is considerably higher in the ulcer group. According to Lewis & Wangenstein (61), celiac ganglionectomy, thoracolumbar sympathectomy and adrenal medullectomy exert no protective effect against histamine-induced ulcer in the dog. Berg *et al.* (62) stated that 60 per cent of rats eating a diet deficient in pantothenic acid developed

ulcers. An antiproteolytic activity of the serum from dogs with histamine-induced ulcer was described by Clifton & Young (63).

According to Pollard *et al.* (64), enterogastrone treatment is ineffective in prolonging the survival time of Mann-Williamson dogs. The enterogastrone was administered orally and parenterally and pre- and postoperatively; no significant differences were noted among the various groups. The use of the Mann-Williamson dog for this type of work is so laborious and prolonged that it would seem advisable for all who contemplate such experiments to have an independent assay of the gastric inhibitory potency of the enterogastrone preparation at the outset and to present these data along with the results of the experiment proper. Benditt *et al.* (65) report that their enterogastrone preparation failed to alter the volume, pH, free acidity, and peptic activity of gastric contents of the Shay rat. They (66) also state that their enterogastrone is mildly antigenic in the guinea pig.

Two methods were described which permit visualization of ulcer-bearing areas. Perl (67) modified the Mann-Williamson operation by substituting an end-to-side gastrojejunostomy with a five-inch stump above the anastomosis for the conventional end-to-end anastomosis of the jejunum and pylorus. The stump is brought to the outside and thus the ulcer area is made available for endoscopic examination. Watman & Nasset (68) devised a technique for the visualization of experimental peptic ulcer in the dog. This involves making a side-to-side anastomosis between a segment of bowel and a Thomas gastric pouch and bringing the proximal portion of the bowel to the exterior as a Maydl type of fistula. An infant proctoscope is easily inserted for visual examination of the stoma ulcer. The animals thus operated, unlike the Mann-Williamson dog, are able to maintain a good nutritive state.

New evidence was presented by Watman & Nasset (69) which appears to implicate the thyroid gland in the regulation of gastric function. Normal guinea pigs injected daily with histamine die of perforated peptic ulcer in 161 ± 35 hr. Thyroidectomy six weeks prior to the administration of histamine reduces survival time to 56 ± 8 hr. Six weeks of pretreatment with thiouracil reduced the oxygen consumption as much as thyroidectomy, but the survival time was 125 ± 29 hr. which is not significantly different from the control values. These results suggest some thyroid activity not related to tyroxine.

PANCREAS

Secretin and pancreozymin.—A new preparation of secretin suitable for tests of pancreatic function in man was announced by Friedman & Thomas (70). It was administered to 150 human subjects without serious reactions. These investigators also published an assay method and some data on the distribution of secretin (71). Nothman (72) reported clinical trials of the secretin preparation referred to above.

Wang *et al.* (73) studied the effects of pancreatic duct ligation on the responses of the gland to secretin and pancreozymin. The ducts were ligated

12 hr. to two weeks before observing the secretory response. Two weeks of duct ligation was sufficient to abolish all responses to secretin and pancreozymin; most of the diminution in response occurred in four days. Histological study revealed a parallel degeneration of secretory cells.

Crick *et al.* (74) reported difficulty in separating secretin from pancreozymin. All previous work had been done with a sample of prewar bile salts and when this ran out it became impossible with a new lot to duplicate the earlier results. Davies *et al.* (75) observed that acetylcholine, secretin, and pancreozymin bring about a rise in oxygen consumption of pancreatic tissue *in vitro*.

Several observations were made by Newman & Eisenstein (76) on a patient with complete external pancreatic fistula. The average 24-hour volume of pancreatic juice was 1,250 ml. Comfort *et al.* (77) measured the pancreatic response to secretin in 13 patients with idiopathic steatorrhea. Volume, bicarbonate, amylase, lipase, and trypsin were all normal. It was concluded that pancreatic dysfunction is not a factor in the steatorrhea of such cases. Myhre *et al.* (78) investigated changes in serum lipase and amylase due to secretin stimulation of the pancreas. In 70 per cent of normal humans, a significant elevation of serum enzymes occurred; patients with advanced pancreatic disease failed to show any change.

Enzymes, composition of juice, and tissue.—Steady progress is being made in elucidating the nature of various pancreatic enzymes as well as the types of substrates which they hydrolyze. Fodor (79) studied the lipase activity of pancreatic extracts and suggests that the pancreas produces at least two different ester-hydrolyzing enzymes. By means of histochemical localization, Gomori (80) demonstrated that most of the triglyceride lipase is found in the pancreas. Lesser amounts are found in the stomach and small intestine.

Snoke & Neurath (81) and Kaufman & Neurath (82) have defined some of the structural requirements of specific substrates for chymotrypsin. Smith & Hanson (83) state that pancreatic carboxypeptidase contains magnesium as an essential constituent of the enzyme molecule. Hanson & Smith (84) demonstrated optical specificity for pancreatic carboxypeptidase.

An unsuccessful attempt was made by Neal *et al.* (85) to demonstrate the presence of insulin in pancreatic juice. Kazal *et al.* (86) claim to have prepared a pancreatic protein fraction which is hyperglycemic. In the rabbit, a dose of 100 to 200 mg. per kg. was sufficient to more than double the concentration of blood sugar. It did not, however, protect mice against insulin convulsions. Wick & Laurence (87) concluded that the "lipocaine action" of pancreatic tissue preparations is due to choline.

SMALL INTESTINE

Absorption.—In the last year a great deal of attention has been given to the absorption of fats and fat-soluble vitamins. Tidwell (88) made a study of fat absorption in the rat. The chylomicron count indicated lipemias of equal intensity whether the animal was fed neutral fat or the free fatty acids

prepared from it. Choline, given either by mouth or intraperitoneal injection, accelerated fat absorption. This investigator suggests that choline may be the limiting factor in synthesizing the phosphatide required in the resynthesis of triglyceride. Becker *et al.* (89), using the technique of the chylomicron count in finger blood, made a comparison between groups of young and old people. The latter maintained elevated chylomicron counts for many hours.

Defective fat absorption following vagotomy in man was reported by Fox & Grimson (90). They arrived at their values for fat absorption by subtracting the fecal fat from the amount ingested. Fecal fat in nine normal subjects averaged 3.0 gm. per day; in the operated patients it was 6.0 gm. per day. Fat absorption ranged from 92 to 97 per cent for normals and 77 to 93 per cent for the vagotomized patients. It is significant that the stool volume for the patients was approximately double the normal value. If the concentration of endogenous fat in the stool were to remain constant, the increased fecal fat in the operated individuals would be accounted for. This possibility was not considered in the interpretation of the data.

Stanley & Thannhauser (91) used a neutral fat labeled with radioactive iodine to study the absorption and disposition of fat in man. At intervals during 24 hr. the amount of iodine in the thyroid, serum, and urine was determined. In the first 2 hr. after feeding the labeled fat, the concentration of "water soluble iodine" in the serum was rather great and this suggests that the intestine may metabolize some fat during absorption. In 24 hr. 50 to 73 per cent of the labeled fat had been metabolized.

Sobel *et al.* (92) stated that newborn children absorb fats, and especially vitamin A in oil, much less efficiently than children one year of age or older. Kagan *et al.* (93) reported that normal children absorb vitamin A alcohol and ester equally well from aqueous dispersions. Kagan *et al.* (94) conclude that children with the nephrotic syndrome utilize vitamin A more slowly than normals and hence their plasma vitamin A remains high for many hours after the normals have subsided. Popper *et al.* (95) reported that plasma vitamin A in human subjects was only slightly more elevated after taking the vitamin in the ester rather than the alcohol form, whether in oil or in water.

The absorption of vitamin A was studied in ruminants and rats by Eden & Sellers (96). The portal blood and lymph glands from different parts of the body were analyzed for vitamin A. Systemic blood always contained more vitamin than portal blood and the intestinal lymph glands more than similar structures in other parts of the body. Searle & Annegers (97) confirmed the old observation that bile is essential for normal fat absorption. Mann *et al.* (98) discovered that rats subjected to complete lymphatic drainage of the intestinal tract develop a bleeding tendency in approximately 18 hr. Vitamin K given subcutaneously prevents the development of this condition or stops it if it has begun. These facts are interpreted to mean that all of the vitamin K in the rat is absorbed by way of the thoracic duct.

The importance of the lymphatic pathway in fat absorption was empha-

sized also by Bloom *et al.* (99). They fed rats palmitic acid labeled with radioactive carbon and were able to recover 81 to 95 per cent of the absorbed labeled palmitic acid in the thoracic duct. It was immaterial whether the compound was fed as the fatty acid or the triglyceride. According to Lassen *et al.* (100), polymerization of sardine oil prevents its digestion and absorption. Storage of vitamin A in the rat after feeding the three provitamins cryptoxanthine, α - and β -carotene was investigated by Johnson & Baumann (101). The absorption of these compounds was determined by subtracting the fecal excretion from the amount ingested. The percentage excretion appeared to be characteristic for each compound. Actually, some overlapping occurred and if one plots percentage retained (absorbed) against dose the points fall on a reasonably straight line indicating 50 to 60 per cent absorption. With the aid of the fluorescence microscope and frozen sections, Volk & Popper (102) demonstrated oil droplets in the intestinal epithelial cells after feeding corn oil. No fluorescence, due to fat, could be demonstrated in either the large bowel or the blood vessels.

Carbohydrate and protein.—Fisher & Parsons (103) described a new method of using the surviving rat intestine for absorption studies. The lumen of the segment of gut is perfused with a solution of the material to be absorbed and the serosal surface of the segment is bathed in an oxygenated saline solution which is circulated in an independent circuit. With the aid of this method, these investigators (104) studied the absorption of glucose. The small intestine was observed to translocate glucose from luminal to serosal side against a concentration gradient and this activity was inhibited by phlorhizin. As glucose passes through the gut wall some of it disappears and presumably it enters the metabolic processes of the surviving tissue. The presence of an absorption gradient was confirmed—a nine-fold difference in the rate of glucose absorption exists between the terminal ileum and a segment 80 cm. above.

Sucrose absorption in sprue was investigated by Fox (105). The method was to give 100 gm. of sucrose by mouth and determine both glucose and fructose in the blood at intervals thereafter. Fructose concentration increased more rapidly than glucose concentration. In the normal subject the fructose declined rapidly after 1 hr. but continued high for about 3 hr. in patients with sprue. These observations would be much more informative if the simple sugars had also been given intravenously in order to have some measure of the rate at which the tissues can dispose of glucose and fructose. From the data as they stand it is impossible to decide whether the absorption of simple sugars in patients with sprue differs from normal.

Christensen & Shwachman (106) suggest the determination of plasma glycine after gelatin feeding as a diagnostic procedure for pancreatic fibrosis. The data from such a procedure should be interpreted in view of the fact that gastric juice contains a gelatinase and that no information is given concerning the rate at which glycine is removed from the blood. An attempt was made by Dent & Schilling (107) to demonstrate whether peptides are

absorbed from the alimentary tract. Portal blood was sampled, by means of a London cannula, at intervals after the feeding of meat. The amino acid pattern, as determined by paper partition chromatography, was qualitatively the same in systemic as in portal blood. No evidence of peptide absorption was discovered. It is interesting that feeding the dog human serum albumin produced a large increase in concentration of amino acids in the portal blood but the feeding of whole dog plasma failed to produce a significant change. This fact recalls the early experiment of Hamburger who discovered that homologous blood serum is readily absorbed from an isolated loop of intestine, presumably without previous digestion.

Blondheim & Kunkel (108) presented evidence that patients with cirrhosis may divert some portal blood through collateral veins in the abdominal wall. After feeding thiocyanate or fluorescein, these substances appeared in certain abdominal veins in higher concentration than in peripheral blood. After feeding *p*-aminobenzoic acid, the acetyl derivative of this compound was found in relatively high concentration in the abdominal collaterals and it was concluded that the intestinal wall is capable of acetylating this vitamin. Crandall (109) demonstrated that barium is absorbed from the alimentary tract of the rat. He points out that this result was not unexpected because barium sulfate is appreciably soluble at body temperature. Zirconium dioxide is completely insoluble and nonabsorbable. This compound is also opaque to x-rays and Crandall suggests that it may find some application in this field. Nordenson *et al.* (110) reported that iron is absorbed more readily as the chloride than the tartrate. Tønnesen (111) reported that atropine is not absorbed from the stomach, is rapidly absorbed from the small bowel, and rather slowly absorbed from the large intestine.

According to Waisbren & Hueckel (112), the absorption of aureomycin is reduced in the presence of aluminum hydroxide. Ch'en & Freeman (113) found that certain ion exchange resins are capable of removing large amounts of sodium, potassium, and calcium from the alimentary tract even when the animals are fed a salt-free diet. Hoffman *et al.* (114) concluded that dehydroisoandrosterone, progesterone, and desoxycorticosterone are absorbed without the aid of bile. Annegers (115) reviewed the literature on the fecal excretion of nutrients in conditions of impaired absorption. Forty-nine references are included.

Too many absorption experiments are planned on the unjustified assumption that the concentration in peripheral blood of the substance being investigated is a direct measure of its absorption. It is trite to remind physiologists that the composition of blood represents an equilibrium between inflow and outflow but many investigators either fail to recognize this fact or choose to ignore it in making interpretations of their data.

Secretion.—Blickenstaff *et al.* (116) studied the secretory responses of two types of duodenal fistula. One was a conventional Thiry type and the other a flap type made by slitting the antimesenteric border and exposing the mucosal surface. The conventional fistula responded to all types of test

meals and to intravenous injection of crude secretin. The flap failed to respond to test meals but gave the same response to crude secretin as the conventional fistula. The investigators conclude that the difference is due to the absence of mechanical stimulation in the flap type fistula. They suggest that in the conventional fistula, the muscular movements result in rubbing together of opposing areas of mucosa and that this stimulus is adequate to excite the secretory cells. Another possibility may be considered, namely, that exposure of the mucosa to room temperature and the evaporation of water from the surface may set up reflex inhibition of gastric evacuation. Conceivably this might be great enough to prevent the blood concentration of humoral agents or secretagogues from attaining threshold values.

Murdock & Nasset (117) produced hypercalcemia in dogs by means of parathyroid extract, calciferol, and intravenous calcium gluconate and noted that the volume of intestinal juice was diminished. The relationship of insulin hypoglycemia to intestinal secretion was investigated by Kneller & Nasset (118). In the fasting state, the dog responds to moderate hypoglycemia with an increased volume and output of enzymes. This result is consistent with the results obtained by others under similar conditions with the stomach and pancreas. If the blood sugar is reduced below 25 mg. per cent, the intestinal secretion is depressed. According to L'Heureux *et al.* (119), radio-active calcium given subcutaneously is secreted almost wholly by the upper half of the small intestine. Very little is eliminated in the colon. Lawrie & Yudkin (120) were unable to demonstrate any adaptation to diet with respect to the amount of alkaline phosphatase present in the rat intestine. Prudden *et al.* (121) report a relationship between the intestinal secretion of lysozyme and the pathogenesis of regional enteritis.

The literature dealing with the subject of gastrointestinal hormones was reviewed by Grossman (122). The bibliography contains 482 items, many of which refer to unpublished work of the author and his associates. The reviewer took this occasion to announce a new hormone alleged to excite the glands of the duodenum. The bases for this claim are some reinterpretations of the data of earlier workers and unpublished results of the reviewer.

Motility.—The movement of fluid through Thiry-Vella loops of intestine was studied by Gregory (123). Feeding the animal (dog) diminished the amount of saline which would flow through the loop at constant pressure and increased the amplitude of contractions. Denervation abolished these responses to feeding. Dreyer & Zander (124) reported a hypermotile phase of intestinal motor activity following immediately after inhibition by epinephrine. The same phenomenon was observed by Chakrabarty (125). McMahon *et al.* (126) described the effects of prostigmine on the motor functions of the human ileum and colon.

Douglas (127) made some interesting observations on changes in frequency of jejunal contractions occasioned by transplantation or simple section and anastomosis. If a segment of jejunum is transplanted to the ileum the rate of rhythmic contraction is reduced 12 to 32 per cent. Simple isolation

as a Thiry-Vella fistula or proximal section with immediate anastomosis yields the same result. Distal section with anastomosis or proximal hemisection are without effect. Bozler (128) reported that the most effective stimulus for the myenteric reflex in the rabbit is longitudinal stretching of the gut; in the dog it is stroking of the mucosa. Bozler (129) described peristalsis as a rhythmic contraction of the bowel which becomes accentuated into a very strong contraction by the presence of a bolus in the lumen.

Northup *et al.* (130) noted that 7.5 per cent carbon dioxide in inspired air reduced the intestinal motility in dogs; at least 15 per cent carbon dioxide was required to affect the same function in rats. Stickney *et al.* (131) found that the distance traversed by a marker in the alimentary tract was a constant percentage of the total length of the tract. Paul & Paul (132) failed to find any effect of mineral oil on the velocity of gastrointestinal transport. Chapman & Palazzo (133) made some observations on intestinal motility in man and attempted a correlation between the type of contractions, as indicated by a balloon system, and the onward movement of barium. Alexander (134) reported the results of experiments on the isolated horse intestine. He made the observation that epinephrine causes a large increase in the tone of the ileum and in the circular fibers of the large intestine.

COLON AND MISCELLANEOUS

Grace *et al.* (135) made observations on a segment of exposed colonic mucosa before and after complete vagotomy. The color, lysozyme and mucus production, and contractile state appeared to be unaffected by the operation. It is suggested that vagotomy *per se* could not be effective in relieving this patient from exacerbations of chronic ulcerative colitis. Grace *et al.* (136) concluded that anger, resentment, hostility, or anxiety are associated with hyperfunction of the colon which, if prolonged, result in increased fragility of the mucosa and spontaneous submucosal hemorrhages. Warren & Sommers (137) failed to find any correlation between the proteolytic activity of feces and the incidence of ulcerative colitis or any other intestinal disease. Victor *et al.* (138) failed to induce ulcerative colitis in the monkey with filtrates of feces.

Grayson (139) used temperature as an indicator of vascular reactions in segments of bowel exposed for colostomy, cecostomy or ileostomy. Vasoconstriction of the skin was accompanied by vasodilatation in the bowel. According to Lee (140), the arterioles in the guinea pig mesentery are always narrowed when the animal is startled. Some arterioles are temporarily occluded with complete capillary staganation of blood. The work of Feldberg & Lin (141) indicates that acetylcholine is synthesized to the greatest extent in the glandular mucosa of the intestine and that, therefore, this substance is produced by the nonnervous tissue of the bowel. This is supported by other work by the same authors (142) which demonstrates that cocaine, nicotine, or D-tubocurarine do not prevent liberation of acetylcholine by the intestine.

Meyer *et al.* (143) report that swine duodenal mucosa contains a substance which, when given with small doses of vitamin B₁₂, is effective in the treatment of pernicious anemia. The significance of the intestinal flora in the nutrition of the guinea pig was clarified by the work of Roine & Elvehjem (144). The results of Block & Stekol (145) prove that radioactive sulfur, fed as sodium sulfate, can be recovered in the cystine and methionine of milk. It is concluded that the synthesis represented by these findings was accomplished by the microorganisms normally present in the rumen. Schweinburg *et al.* (146) demonstrated that, under certain conditions, repeated intraperitoneal infusions may lead to migration of intestinal bacteria to the peritoneal cavity.

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LIVER¹

By J. WALTER WILSON

Department of Biology, Brown University, Providence, Rhode Island

This review is written primarily from the point of view of histophysiology—the relation of function to structure in the organ, tissues, and cells. A comprehensive discussion of the liver, its physiology, and pathology by Lichtman in "Diseases of the Liver, Gallbladder, and Bile Ducts" has been brought up to date in a new and revised edition (1).

STRUCTURE AND CIRCULATION

Elias (2, 3) has presented a detailed study of the structure of the mammalian liver which indicates that it will be necessary to revise the oversimplified description in the current text books. The parenchymal tissue, instead of being in the form of anastomosing cords, is a spongework of anastomosing plates with the thickness of a single cell. The bile capillary system is a continuous network throughout the parenchyma.

Wachstein & Zak (4) demonstrated, with the aid of the histochemical phosphatase method, intracellular bile canaliculi in rabbits following experimental biliary obstruction. They also believe they have shown them to exist in livers of normal rabbits. On the other hand, Adams (5), also using the alkaline phosphatase technique on rat and human livers, could find no conclusive evidence of intracellular terminations of bile canaliculi.

The existence of the perisinusoidal spaces, the spaces of Disse, has been questioned by Popper (6). He compared sections of liver from biopsies taken shortly before death with autopsy material and found that in cases of instantaneous death no such spaces are to be found. They appear only as agonal changes, in cases where the process of death was prolonged by a period of suffocation of ten minutes or longer. He believes, therefore, that they are artifacts.

Elias, has, in general, accepted the features of the hepatic circulation described by Knisely, Bloch & Warner by means of transillumination techniques. These have been presented comprehensively (7), and support the concept of intermittent activity of the mechanisms of circulation, so that blood in the sinusoids is sometimes predominantly venous and sometimes arterial, sometimes stationary and sometimes flowing freely at various speeds.

Julian & DeOme (8) and Deakins & Sugiura (9) have studied plastic casts of the blood vessels of livers of cattle and rodents respectively. They both emphasize the extensive capillary plexus from the hepatic artery surrounding the branches of the bile duct in the portal canal.

¹ Because of limitation of space, the following topics could not be included in this review: carbohydrate and lipid metabolism, experimental liver damage other than dietary, carcinogenesis, thyroid effects, the reticuloendothelium, and bile secretion.

Markowitz (10) successfully tied the hepatic artery of dogs after giving them penicillin. He concluded that the death of dogs with the hepatic artery tied is due to the growth of anaerobic bacteria. Such animals develop massive hepatic necrosis. With penicillin, the dogs survive indefinitely and possibly develop a collateral circulation. Bollman (11) points out that there are other sources of arterial blood in the dog liver than the hepatic artery. Though small in amount, blood from these secondary sources is distributed to every lobe in the liver. This is shown by x-ray pictures after injection of a barium acacia mass through the aorta with the hepatic artery tied.

Thomas & Essex (12) have investigated the sphincter mechanism responsible for the hepatic congestion following intravenous injection of extract of *Ascaris suum* in the dog. By the insertion of a polythene tube into the hepatic vein from the vena cava they found that the drop in the systemic venous pressure extended well beyond the junction of the hepatic veins and the vena cava, which indicates that there is no single sphincter in this region. Casts of the hepatic vein and its branches made with vinyl acetate show bands of constriction arranged in spiral fashion, more pronounced in the smaller vessels. The mechanism seems, then, to be a diffuse spasm of the entire hepatic venous side of the vasculature of the liver. Similar evidence has been found in anaphylaxis and histamine shock, and, in the cat and rat, after injection of the ascaris extract. They present a detailed review of the literature on such mechanisms in the hepatic veins.

Bradley (13) has reviewed the work done on hepatic blood flow by catheterizing the hepatic vein with a radio-opaque catheter inserted in the antecubital vein and measuring the rate of removal of bromsulfalein infused into the blood. He emphasizes particularly the role of the liver in cardiovascular dynamics. By this technique, Bradley, Ingelfinger, Groff & Bradley (14) have shown that the hepatic blood flow tends to be low or normal, never increased, in cirrhosis of the liver, regardless of etiology, and that difference between the arterial and hepatic venous oxygen is usually increased. Bradley (13) attributes this increased oxygen extraction to a more sluggish flow of blood through active tissues.

Blondheim & Kunkel (15) have studied the portal blood in collateral veins of patients with cirrhosis. Portal origin of blood in abdominal collateral veins was demonstrated by feeding fluorescein or thiocyanate, and finding higher concentrations in the abdominal veins than in the antecubital veins.

Kelty *et al.* (16) investigated by reconstruction the relation of the blood vessels to the regenerated hepatic nodule in cirrhosis. The model shows that walls of the hepatic veins are pressed in and their lumens distorted by the neighboring nodules of regenerating tissue. He believes it probable that many branches of the portal and hepatic veins may have been obliterated completely under similar conditions. He would explain the intrahepatic portal obstruction of the cirrhotic condition on the basis of the effects of the dynamic and expansive force of these nodules on the venous circulation. The

blood supply of the regenerative nodule is largely arterial, which, by its higher pressure, can compete more successfully with growth pressure within the parenchyma. Breedis & Young (17) have shown that not only regenerative nodules but also experimental hepatomas have, as they become established, an arterial blood supply.

GROWTH AND MITOSIS

McKellar (18) has described the postnatal growth of the liver of the rat. The mitotic activity was determined with the aid of colchicine. Immediately after birth, there is a period of mitotic quiescence coextensive with the regression of hemopoiesis and the assumption of normal hepatic function. From the second to the eighth week is the primary growth phase with rapid cell proliferation in which the liver increases in weight 500 per cent. This is followed by a secondary phase of slow cell hypertrophy in which in 15 weeks it increases only 150 per cent in weight. Binucleate cells increase in number during the primary phase, then decrease toward its termination with their replacement by polyploid cells. In the primary phase, compound lobules are formed by growth of simple lobules. They are subdivided again into simple lobules by the ingrowth of portal canal tissue.

Wilson & Leduc (19) have discussed the occurrence and formation of binucleate and multinucleate cells and polyploid nuclei in the liver of the mouse. They conclude that binucleate cells may arise by the mitotic division of the nucleus with failure of the cytosome to divide. Binucleate and large multinucleate cells may also arise by fusion of cells. Large nuclei may be produced by the fusion of smaller nuclei or by endomitosis. Magrini (20) has counted chromosomes in squash preparations of livers of rats regenerating after partial hepatectomy. In favorable metaphase plates she finds the diploid number to be 42 and confirms the conclusions of previous workers that a larger class is tetraploid with counts from 80 to 84, and a few very large nuclei are octoploid, although accurate counts could not be made.

The frequent occurrence of abnormal mitotic figures in the liver of the mouse has been reported by Wilson & Leduc (21) when mitosis is induced in a variety of ways. Tripolar and multipolar figures seem to arise when trinucleate or multinucleate cells divide. Fusing telophase nuclei occur when the anaphase movements of the chromosomes fail to separate the daughter groups. Lagging chromosomes may result in bridges of chromatin connecting daughter nuclei, and must result in abnormal division of chromosomes between them.

Miszurski & Doljanski (22) report that colchicine induces mitotic activity in the rat liver. After a single intraperitoneal injection, mitosis is most abundant on the third day, and the figures are normal. Abnormal figures are reported after repeated injections. These are due to the suppression of the mitotic process by colchicine. The authors conclude that polyploidy may arise from the division of chromatids where the process of mitosis has been blocked by colchicine. Wilson & Leduc (23) have investigated the

effect of biotin on the mitotic activity of the liver of the mouse. Although mitosis declined during the development of biotin deficiency and was then increased by treatment, no effects were found that could not be attributed to factors other than biotin. A slight stimulation of mitotic activity was found in the livers of normal mice after subcutaneous injection of biotin. This is attributed to a direct effect of pure biotin, even in the presence in the liver of an abundance of biotin in combined form.

Leduc (24) has investigated the mitotic activity in the liver of the mouse during inanition followed by refeeding with different levels of protein. The mitosis normally present in the livers of young mice disappears during fasting and reappears on refeeding. In adult mice that are refed after fasting, mitosis is initiated in the liver. A change from a low protein to a high protein diet is followed by a wave of mitotic activity. Under varying conditions, the increase in mitotic activity appears to correspond in time to the increase in liver proteins and coincides with the return of basophilic material to the cytoplasm of the liver cells.

The growth and mitotic activity of the liver after coramine feeding, reported by Brazda & Coulson (25) in the rat has been investigated in the mouse by Wilson & Leduc (26). When mice are fed a diet containing 1 per cent coramine, their livers grow rapidly by active mitosis. There is no destruction of cells, but, particularly in the central zone of the lobule, the hepatic cells become distended with hydropic vacuoles. It is pointed out that, in many cases where mitotic activity is induced in the liver, it is preceded by a hydropic vacuolization of the cells.

Bucher, Scott & Aub (27) have reported that, after partial hepatectomy of one individual of a parabiotic pair of rats, mitotic activity was induced in the intact liver of the nonhepatectomized partner in from 48 to 72 hr.

Yeakel (28) has studied the increased weight of livers of tumor-bearing rats. She found the weight of the liver relative to body length increased when the tumor weighed over 30 gm., and when the body length of the rat was over 175 mm. She suggests that the enlargement of the liver is connected with protein metabolism in the growth of the tumor, and that the fact that it does not occur in smaller, younger rats may be explained by the supposition that these animals were still engaged in rapid body growth so that their livers were already enlarged to the physiological maximum.

THE LIVER CELL

With the aid of the electron microscope, phase microscopy, differential centrifugation of particulate materials, ultraviolet spectrophotometry, and the cytochemical visualization of enzyme activity, great steps have been taken toward the development of a picture of the liver cell as a functioning unit. Because of the uniformity of its parenchyma and the relatively small amount of stroma, as well as the great diversity of its activities, the liver occupies a preëminent place in the enzyme studies of the biochemist. Enzyme activities have been investigated with slices, particulate fractions, and

extracts. It is to be emphasized, that, important as it is, the work of the enzyme chemist must be applied with caution to the normal functioning cell of the intact organism. Deane *et al.* (29) have shown that only the peripheral cells in a liver slice produce glycogen. Opie (30) has studied the effects of immersion of small pieces of liver in various media including Krebs-Ringer solution. Striking changes occur immediately after immersion of the liver tissue in the solution, involving particularly the cytoplasmic basophilia and mitochondria with which so much of the enzyme activity of the cytoplasm seem to be associated. Having in mind the precautions necessary to isolate mitochondria with even a semblance of their normal appearance, one wonders what the effect of a prolonged sojourn in a Warburg flask must be.

In spite of all this, however, the work of the enzyme chemist is making an important contribution to the picture as a whole. Claude (31), Schneider (32), Bradfield (33) and Monné (34) have all presented comprehensive reviews in which the present status of the picture is presented.

NUCLEI

Dounce (35) has improved the technique of isolating nuclei by differential centrifugation, particularly in the cold at pH 6, and has presented a review of the literature of the subject. Dounce & Beyer (36) have used nuclei isolated from liver, kidney, and pancreas in a study of the distribution of arginase. The arginase activity of nuclei from kidneys, pancreas, and chicken liver is extremely small or zero. The activity of arginase per dry weight of nuclei isolated from rat liver cells is slightly higher than the corresponding activity per dry weight of whole rat liver. They suggest that since the role of arginase is mainly in the formation of urea, which presumably occurs in the cytoplasm of the liver cells, its occurrence in the nucleus may indicate that it is synthesized there.

MITOCHONDRIA

The technique of the isolation of mitochondria has been perfected with the introduction of 0.88 *M* sucrose as a medium for suspension [Hogeboom *et al.* (37, 38)]. With this medium the particles retain their elongate rod-like shape and also the staining properties characteristic of mitochondria. They suggest that the effectiveness of this solution in place of 0.85 per cent sodium chloride is due to its high osmotic pressure, and that the osmotic pressure within the living hepatic cell, at the mitochondrial membrane, may be higher than the blood osmotic pressure.

A somewhat similar concept of the mitochondria in relation to osmotic pressure has been developed by Opie (30, 39). He has studied the effect of immersion of small pieces of liver in various media, including 0.15 *M* sodium chloride, potassium chloride, and calcium chloride, as well as Krebs-Ringer solution. He concluded that the changes observed are due to osmotic effects

of the solutions. The osmotic pressure within the liver cell is apparently slightly more than twice that of the blood and erythrocytes. With injury (e.g., by chloroform or by carbon tetrachloride) the mechanism which maintains this difference fails and the osmotic pressure within the cells falls, leading to the characteristic changes of the mitochondria: swelling, rounding-up, and loss of staining characteristics.

The structure of the mitochondria has been investigated with the phase microscope and the electron microscope. Zollinger (40) found the mitochondria easily observed in living cells under the phase microscope. They swell into vesicles when the cells are in a hypotonic medium, which indicates the presence of a semipermeable membrane and, indeed, a membrane can be seen separated from the slightly swollen "body" of the mitochondrion when the cells are immersed in distilled water. In a later paper (41) he attributes the "cloudy swelling" of the pathologist to swelling of the mitochondria due to a disturbance of the permeability of the cell membrane which leads to altered intra- and extracellular osmotic conditions.

Dalton *et al.* (42) studied mitochondria isolated from the livers of mice by differential centrifugation both in 0.85 per cent sodium chloride and 0.88 *M* sucrose. They observed a surface membrane which in some instances was wrinkled and torn. By the use of solutions with varying osmotic pressure they showed it to be semipermeable. They conclude that the mitochondria are not simply coacervate in nature. They attribute the variation in mitochondrial size, shape, and number under varying physiological conditions to changes in colloid osmotic pressure of the cytoplasm.

Roberts (43), in a more conventional study, has described the changes in form of the mitochondria of the liver of *Ambystoma* subjected to long exposure to cold. He expresses the doubt that these changes reflect the alteration of some specific role of the mitochondria in the vital processes, but suggests rather that they are an expression of an alteration of the normal cellular metabolism.

Kennedy & Lehninger (44), using mitochondria of rat liver prepared by differential centrifugation in 0.88 *M* sucrose, have shown that the mitochondria contain the complex enzyme systems responsible for the oxidation of fatty acids and Krebs cycle intermediates and esterification of phosphates that Friedkin & Lehninger (45) and Lehninger (46) had shown to be coupled with these oxidations. The mitochondria are not, however, completely autonomous in these activities because they must be supplemented with certain cofactors such as adenosinetriphosphate and magnesium ion. The mitochondria have, furthermore, almost no glycolytic activity, so are dependent for such preparatory metabolic activity on the general cytoplasm.

Previous investigators [Schneider (32)] have located all or nearly all of the other oxidative systems of the cell in the mitochondria which would seem to justify Claude's characterization of them as "the power plants of the cell."

MICROSOMES, NUCLEIC ACIDS AND PROTEINS

A second class of particulates isolated from the cytoplasm is the submicroscopic fraction, the microsomes. Because of their high ribonucleic content, these are responsible for the basophilia of the cytoplasm of the liver cell. They may be aggregated into masses with more or less indefinite boundaries or may appear as fine fibrils which are sometimes aggregated into larger masses. These basophilic inclusions have been considered by many [e.g., Sibatani (47)] to be artifacts, but Lagerstedt (48) has found them in sections prepared by the freezing-drying technique with the same morphological features as in material fixed in Carnoy's fluid. He believes, therefore, that they exist as such in the living cell, and that Claude's microsomes may be these basophilic cytoplasmic inclusions disintegrated mechanically during manipulation. On the other hand, in electron micrographs of ultra-thin sections of guinea pig liver, Claude & Fullam (49) show particles of the right size distributed throughout the cytoplasm which they consider to be the microsomes. Dalton *et al.* (50) have reported ultramicroscopic filaments in the cytoplasm of liver cells, revealed by the electron microscope in ultra-thin sections of material fixed in osmic acid or Regaud. These suggest that, under certain circumstances at least, the microsomes may be aggregated into filaments at the submicroscopic level. Rich & Berthrong (51) have described strongly basophilic cytoplasmic bodies in hepatic and adrenal cells of man in acute infections. They contain ribonucleoprotein. They may also be aggregates of the submicroscopic particles, but larger, more compact, and perhaps more discrete than usual. It is suggested that they may be an expression of an increased activity of some normal function of the cell.

Opie (52) has observed under various conditions the concentration of ribonucleic acid-containing, basophilic material on the surface of the large cytoplasmic granules. It is either a component of the membrane or shell of the mitochondrion, or material adsorbed onto its surface. Leduc (53) has reported similar basophilic rims around cytoplasmic granules in the hepatic cells of the mouse after a prolonged fast. Sibatani (47) has also described enlarged bodies with basophilic rims giving the cytoplasm of the rat liver cell a foam-like appearance in certain "catastrophic" conditions, including prolonged starvation.

Because of the basophilic material in its cytoplasm, with its ribonucleic acid content and its lability under various physiological and pathological conditions, and also because, although all of its nuclei are usually in the resting state, large numbers of them may be stimulated to mitotic activity, the liver cell has played an important role in discussions of nucleic acid and protein metabolism. Brachet (54, 55) and Caspersson (56) have recently summarized their views on this subject. A complete discussion would carry this review too far afield. The literature on the content and distribution of the nuclei acids in the liver cell and its components is summarized by Davidson (57).

Marshak (58) has investigated the nature of the P^{32} -containing material of nuclei of livers of normal rats and rats with actively regenerating livers, after the injection of P^{32} as Na_2HPO_4 . After 3 hr. little or none of the P^{32} appears either in DNA (desoxyribonucleic acid) of the mitotic nuclei and in RNA (ribonucleic acid) of nonmitotic cells. He considers that a precursor of both is formed. There may be two processes competing for the newly-formed precursor: mitosis and the cytoplasmic activity involving the basophilic materials of the cytoplasm on which the synthesis of proteins depends. Brachet (55) has emphasized that the cytoplasmic basophilia rapidly decreases in mitotically active cells, even when it is high in adjacent cells.

By differential centrifugation, Marshak & Peck (59) have been able to separate the isolated nuclei of the liver into two fractions, one containing the nuclei of the hepatic cells, and the other the nuclei of the fibroblasts, reticuloendothelial and endothelial cells, and the leucocytes. Three hours after intravenous administration of P^{32} , the specific activity of these two classes of nuclei indicates that the nucleic acid turnover in the hepatic cells is more rapid than that of other cells in the liver.

Stowell (60) studied the correlation between changes in cellular structure and nucleic acid concentration during the first two days of regeneration of rat liver after partial hepatectomy. By 24 hr. the mean volumes of cytoplasm, nucleus, and nucleolus had increased. With the increase in cell division at 24 to 30 hr., these volumes dropped, that of the nucleolus returning to normal in 48 hr. Ultraviolet cytochemical methods showed no increase in nucleic acid in the first day, but with the onset of rapid cell division in the second day there was an increase in nucleic acid concentration in the cytoplasm near the nuclear membrane and in the nucleolus.

Novikoff & Potter (61) have shown by chemical methods that although the DNA content of regenerating liver undergoes no consistent change, the RNA concentration is markedly increased during the period of the second and third days when the growth of the liver and mitotic activity is at its greatest height.

Vendrely & Vendrely (62) studied the variation in the ribonucleic acid and the mitochondria of the liver cells of rats on a protein-free diet, chemically and cytologically, in homogenate, in isolated mitochondria, and in sections. After forty days, the animals had lost weight and the liver had decreased in ribonucleic acid content, but the chondriome did not vary in quantity nor in RNA content. The loss of hepatic RNA thus seems to affect the microsomes exclusively.

Berg (63), who studied the behavior of the basophilic granules in the liver cytoplasm during starvation, suggested that they might represent a reserve protein, and accordingly have a specific storage function like fat globules and glycogen masses. Chemical investigations of the materials lost from the liver cell during starvation have shown, however, that no single protein is involved that can be designated a storage protein. Luck (64) has

presented and discussed the problem in a review of the liver proteins. One difficulty is that the liver proteins are still not well characterized. He emphasizes that the whole subject of fractionation of liver proteins is new. Although extensive studies are under way in various laboratories, only fragmentary reports have appeared in the literature.

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The concept of a dynamic state of the body protein, in which the proteins of cells and plasma are in a dynamic equilibrium, has been reemphasized by Borsook (68). Sprinson & Rittenberg (69), by studying the rate of interaction of N^{15} -labeled glycine with the body proteins in rats and man, have been able to calculate the rate of protein synthesis and the size of the nitrogen pool. Peters & Anfinsen (70) have shown that when chicken liver slices are incubated in C^{14} -labeled carbon dioxide-bicarbonate medium, dicarboxylic amino acids and alanine are incorporated into serum albumin, and this albumin is released into the surrounding medium.

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Marshak (58) has investigated the nature of the P^{32} -containing material of nuclei of livers of normal rats and rats with actively regenerating livers, after the injection of P^{32} as Na_2HPO_4 . After 3 hr. little or none of the P^{32} appears either in DNA (deoxyribonucleic acid) of the mitotic nuclei and in RNA (ribonucleic acid) of nonmitotic cells. He considers that a precursor of both is formed. There may be two processes competing for the newly-formed precursor: mitosis and the cytoplasmic activity involving the basophilic materials of the cytoplasm on which the synthesis of proteins depends. Brachet (55) has emphasized that the cytoplasmic basophilia rapidly decreases in mitotically active cells, even when it is high in adjacent cells.

By differential centrifugation, Marshak & Peck (59) have been able to separate the isolated nuclei of the liver into two fractions, one containing the nuclei of the hepatic cells, and the other the nuclei of the fibroblasts, reticuloendothelial and endothelial cells, and the leucocytes. Three hours after intravenous administration of P^{32} , the specific activity of these two classes of nuclei indicates that the nucleic acid turnover in the hepatic cells is more rapid than that of other cells in the liver.

Stowell (60) studied the correlation between changes in cellular structure and nucleic acid concentration during the first two days of regeneration of rat liver after partial hepatectomy. By 24 hr. the mean volumes of cytoplasm, nucleus, and nucleolus had increased. With the increase in cell division at 24 to 30 hr., these volumes dropped, that of the nucleolus returning to normal in 48 hr. Ultraviolet cytochemical methods showed no increase in nucleic acid in the first day, but with the onset of rapid cell division in the second day there was an increase in nucleic acid concentration in the cytoplasm near the nuclear membrane and in the nucleolus.

Novikoff & Potter (61) have shown by chemical methods that although the DNA content of regenerating liver undergoes no consistent change, the RNA concentration is markedly increased during the period of the second and third days when the growth of the liver and mitotic activity is at its greatest height.

Vendrely & Vendrely (62) studied the variation in the ribonucleic acid and the mitochondria of the liver cells of rats on a protein-free diet, chemically and cytologically, in homogenate, in isolated mitochondria, and in sections. After forty days, the animals had lost weight and the liver had decreased in ribonucleic acid content, but the chondriome did not vary in quantity nor in RNA content. The loss of hepatic RNA thus seems to affect the microsomes exclusively.

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Campbell & Kosterlitz have continued to develop the idea of a "labile liver cytoplasm" formulated on the observation that proteins and phospholipids vary together under all conditions of growth, and with protein content of the diet. They (73) have found this relation so constant that they have used it to assess the nutritive value of proteins, and have obtained values comparable to those obtained by other methods. They (74) found that at least 60 per cent of the excess nitrogen lost in the urine in the first few days after an animal is placed on a protein-free diet can be accounted for by the nitrogen derived from the proteins, nucleic acid, and other nitrogenous substances of the liver, and point out that this further supports the idea of mobilization of a labile liver cytoplasm.

Investigation of enzyme activity in the livers of rats during the fluctuation of protein in starvation and on protein-free diets [Miller (75), Seifter *et al.* (76) and Harkness *et al.* (77)] has led to the conclusion that not only the activity of the enzymes but the levels of vitamins have a linear relation to the concentration of liver nitrogen. This suggests that the vitamins exist in combined form in the liver, and not as free vitamins. The diminution of enzyme activity seems to be due to loss in enzyme protein per se. As Miller (75) points out, the fact that cell size, "labile liver cytoplasm", cell protein, phospholipin and ribonucleoprotein, as well as enzyme activity, decrease in roughly parallel fashion, supports a concept of intracellular functional units made up of a variety of enzymes, and associated with nucleoprotein and lipoprotein, and implies that the loss of any integral part of the unit is associated with the loss of a unit as a whole.

Lagerstedt (48) has presented a complete review and a new detailed study of the changes in the cytological appearance of the basophilic materials in the liver of the rat during starvation, feeding of low protein diets, and refeeding with high protein diets. The nucleolus and the nucleolo-associated chromatin diminish rapidly in starvation and increase rapidly with the feeding of a high protein diet. The basophilic cytoplasmic inclusions react similarly, but always more slowly. In starvation they completely disappear, and when they first reappear it is in close contact with the nuclear membrane. He believes that the basophilic cytoplasmic inclusions represent the entire amount of protein which in chemical analysis is found to be lost under starvation and on a low protein diet. This is not discussed from the point of view of the labile liver cytoplasm of Kosterlitz & Campbell, or of our knowledge of the enzyme content of the microsomes. He has considered it largely from the point of view of nucleic acid metabolism, and its relation to protein synthesis. Protein synthesis is initiated in the nucleolar mass through the building up of nucleolo-associated chromatin. The nuclear chromatin shifts to the neighborhood of the nuclear membrane, and the nucleic acid containing proteins are built up in the cytoplasm on the opposite side of the nuclear membrane, giving rise to the basophilic inclusions. The morphological features of these inclusions and nucleolar apparatus are thus indicators of the protein metabolism of the cells.

PHOSPHATASES

The development of cytochemical methods for the visualization of enzyme activity in histological sections has made it possible to study the distribution of this activity in organs, tissues, and cells and to a certain extent to estimate its intensity. These results can be compared with the quantitative studies of the biochemist. The phosphomonoesterases (alkaline and acid phosphatases), esterase (lipase) and β -glucuronidase have all been studied in the liver.

Critical studies of Lison (78), Martin & Jacoby (79), Gomori (80, 81, 82), and Newman *et al.* (83) have made a great progress toward establishing the validity of the cytochemical alkaline phosphatase technique from the point of view of localization and of specificity with respect to substrate. The distribution and intensity of alkaline phosphatase in the liver have been found to vary in different species [see the summary by Newman *et al.* (83)]. Sulkin & Gardner (84) report that the hepatic cell of the rat shows a variable reaction for acid phosphatase in the cytoplasm but a more constant one in the nucleus, mostly in the chromatin and nucleoli. For alkaline phosphatase the reaction is usually lacking in the cytoplasm and the bile canaliculi, while the nucleus shows activity in high degree, principally in the nuclear membrane and nucleoli. During regeneration after partial hepatectomy they found acid phosphatase activity increased in the nuclei of the hepatic cells but unchanged in the cytoplasm. Alkaline phosphatase activity was present in the cytoplasm of all hepatic cells with marked activity in the bile canaliculi and nuclei. The increase in the nuclei they consider as additional evidence of the importance of the phosphatases in nucleoprotein metabolism. Rosenthal *et al.* (85) report that increase in alkaline phosphatase occurs also in the regenerating liver after partial hepatectomy in protein depleted rats. Rabinovitch (86) reports that in the guinea pig liver the nucleolus itself exhibits no evidence of acid phosphatase activity but the "nucleolus associated chromatin", which in the theory of the Swedish school plays an important role in nucleoprotein metabolism, always stains.

Kochakian & Bartlett (87) found increased alkaline phosphatase, determined biochemically, in the livers of fasted rats injected with adrenal cortical steroids. Since they obtained no corresponding increase when fasted rats were fed a high protein diet, Kochakian, Bartlett & Moe (88) suggest that the increased alkaline phosphatase is associated with an increased glyconeogenesis from endogenous protein. Herlant & Timiras (89) found in the alarm reaction in rats an increased alkaline phosphatase activity in the liver and lymphatic tissue. They point out that this appears to parallel the increased metabolism of these tissues during stress and would serve to indicate a close relationship between alkaline phosphatase and cortical secretion in the alarm reaction.

The occurrence of alkaline phosphatase in the bile and its rise in the plasma in obstructive jaundice present a problem as to the role of the liver cell in its production and secretion. The two points of view are that the liver

cell is the main site of production of the enzyme which it then secretes in the bile or that the enzyme is produced in other tissues such as bone from which it is liberated into the plasma, the role of the liver cell being merely to transport it to the bile.

Cantarow & Miller (90) and Wang & Grossman (91), on the basis of similar experiments, have come to the conclusion that the normal liver cell does not remove alkaline phosphatase from the blood in significant amounts. Hence the liver must produce it. Serum high in alkaline phosphatase from a donor dog with obstructive jaundice was transferred to a normal dog with no significant rise in enzyme content in the bile, although the level in the blood remained high for some time.

Kritzler & Beaubien (92) studied the alkaline phosphatase activity in livers of dogs with experimental biliary obstruction. They found that bile capillaries distended until they made contact with the spaces of Disse and consider this the channel through which the enzyme enters the circulation by way of the lymph. They lean toward the view that the liver cell is excreting the material. Hard & Hawkins (93), in similar studies on the rabbit, describe the dilated bile capillaries as expanding between the hepatic cells eventually reaching the sinusoids. This permits the escape of phosphatase into the blood. They believe the enzyme is produced in the liver cell continually, thus producing the rise in level in the serum.

Wachstein & Zak (94) have reviewed the whole subject of alkaline phosphatase in experimental biliary cirrhosis and on the basis of their own experiments with both dogs and rabbits conclude that there is no evidence that the distension of the bile capillaries leads to true breaks that would account for the regurgitation of bile. They conclude that the role of the liver is primarily that of a regulatory organ concerned with the excretion of surplus phosphatase.

Dalgaard (95) reports that in dogs neither the removal of the duodenum-pylorus nor of the small intestine prevents the increase in serum alkaline phosphatase which occurs following ligation of the common bile duct. This indicates that the intestine is not the source of the increased phosphatase. He has also shown (96) that in dogs with a biliary fistula there is no marked increase in serum phosphatase, hence the increase that occurs in biliary obstruction cannot be due to the absence of bile in the intestine. The amount removed in the bile is adequate to account for the increase in the serum after biliary obstruction. In a third paper (97) he concluded that, because after complete hepatectomy there is an increase in serum phosphatase, the liver must act primarily as a regulator of phosphatase excretion. Flock & Bollman (98) found that the increase in alkaline phosphatase of intestinal lymph following feeding of a fat-containing meal is abolished with ligation of the bile duct or biliary fistula. Hence, bile in the intestine is somehow involved in the transport or release of alkaline phosphatase from the intestinal mucosa.

ESTERASES

The two enzymes, true lipase and the non specific esterase of the liver, kidney, and other tissues overlap somewhat in their activity. The optimum conditions of lipase activity are generally found with esters of acids with eight or more carbon atoms, whereas the nonspecific esterase acts best with esters of three-carbon acids. That Gomori's (99) original histochemical method for demonstrating lipase activity in tissues is not specific for either enzyme was pointed out by Huggins & Moulton (100) and Nachlas & Seligman (101, 102). The substrates, Tween 40 or 60, are polyglycol esters of palmitic and stearic acids. Nachlas & Seligman (101) suggest that the same conditions, a large number of hydroxyl groups on the alcohol, that make these esters water-soluble, make them susceptible to attack by the esterase. Gomori (103) has recently shown that the true lipase can be differentiated from the nonspecific esterase histochemically by the use of Tween 80, which has the unsaturated oleic acid rather than the saturated acids of Tween 40 and Tween 60. Nachlas & Seligman (101) have devised a new histochemical method for the demonstration of these enzymes, using β -naphthyl esters as substrates, and by coupling the β -naphthol liberated by the enzymatic hydrolysis with a tetrazonium salt producing an azo dye that reveals the site of enzyme activity.

There is a considerable amount of esterase activity in the liver, particularly in the central portion of the lobules [Gomori (99)], but little in the Kupffer cells or bile duct epithelium [Nachlas & Seligman (104)]. The latter point out that the distribution of the esterase in the body gives us no clue to its function in the body. Huggins & Moulton (100) found much less esterase in all tissues of the new born rat up to four to five days than in the corresponding tissues of adults, but that the adult concentration was rapidly arrived at in all tissues except the testis. Omachi, Barnum & Glick (105) have shown that in the fractions separated from the mouse liver by differential centrifugation, a large part of the esterase activity of the liver is found in the microsomes.

Koch-Weser *et al.* (106) have reported a sharp drop in liver esterase in livers of rats injured by carbon tetrachloride in which there is considerable fatty infiltration. They emphasize that the fatty infiltration appears first. Mark (107) has studied, with Gomori's technique, the distribution of esterase in preneoplastic and neoplastic states induced in rat liver by *p*-dimethyl-aminoazobenzene. He found that there is no reaction in areas of fatty degeneration or heptatomas, and that in hyperplastic nodules it is weak or absent.

 β -GLUCURONIDASE

A method for the histochemical localization of glucuronidase has been developed by Friedenwald & Becker (108). This enzyme, which catalyzes the hydrolysis of the glucuronide linkage, has been considered to play a part in the formation of glucuronides in the body [Fishman (109)]. This process

takes place, however, only in the liver and kidney, whereas the β -glucuronidase is present in every tissue so far examined, and the Edinburgh group (110 to 114) has produced convincing evidence that the enzyme is not responsible for glucuronide formation but that its activity reflects the state of proliferation of the tissue. Levvy *et al.* (110) attempted to confirm Fishman's (109) observation that in mice fed menthol, the β -glucuronidase activity of the liver, spleen, and kidney was increased. They found, after a single interperitoneal injection of menthol, a rapid rise in glucuronidase activity in the liver, but only later in the kidney and not at all in the spleen. They state that the rise in enzymatic activity in the liver reached a maximum after 24 hr. and persisted seven days. This coincides with the appearance and repair of damage. Furthermore, following administration of a variety of toxic agents, there was a rise in β -glucuronidase in the liver or kidney, depending on the organ or organs attacked. The increase is, in general, associated with active cell proliferation induced by the injury rather than the injury itself. High values occurred in the livers of adult mice after partial hepatectomy and in the liver, spleen, and kidney of infant mice.

Kerr, Campbell & Levvy (111) report that colchicine reduces the glucuronidase activity of the liver in infant mice but not in adult mice. However, in adults it prevents increase in enzyme activity at the same time that it prevents the stimulation of mitosis under various conditions. Thus, the action of the drug on the enzyme seems to be secondary to its effect on mitosis.

Karunairatnam & Levvy (112) and Karunairatnam, Kerr & Levvy (113) have shown that in liver slices there is an enzyme system responsible for glucuronide synthesis which can be clearly distinguished from β -glucuronidase. The latter is inhibited by saccharic acid, the former not. Saccharic acid does not, however, affect the proliferation of liver cells in livers of young mice or in regenerating liver. None of the measures that increase mitotic activity in the liver have any effect on glucuronide synthesis by liver slices.

Friedenwald & Becker (108) have described two methods for the histochemical localization of β -glucuronidase activity, and state that in the rat it occurs in the hepatic cells and not in the blood vessels of the liver. It appears in the cytoplasm rather than in the nucleus.

Campbell (114) used these histochemical techniques to study the distribution of the activity in the mouse tissues and tumors. He reports that the intracellular site of the enzyme in liver and kidney appears to be coincident with the mitochondria. The activity in the kidney is in the proximal convoluted tubules. The reaction is more intense in males than in females, and diminishes with castration in males. Campbell also reports that the activity is high in malignant tumors, and is mainly localized in anaplastic areas where cell division is prominent. This is in keeping with the reports of earlier workers.

HORMONES

The inactivation of α -estradiol by liver slices is complete but homogenate is much less effective [DeMeio *et al.* (115) and Coppedge *et al.* (116)]. The

addition of a boiled saline extract of rat liver, or of diphosphopyridine nucleotide (DPN), raises the activity of the homogenate to that of the slices. Nicotinamide, which protects DPN, preserves the estrogen-inactivating ability of the liver. The inactivation is, therefore, enzymatic and linked to DPN. At least part of the α -estradiol is oxidized to estrone, and very little, if any, is conjugated as sulfate or glucuronide [Pearlman & DeMeio (117)].

Paschkis & DeMeio (118) found good inactivation of α -estradiol by liver slices of six-day rats, slices of livers injured by 2-acetylaminofluorene and slices of hepatomas produced by 2-acetylaminofluorene and *p*-dimethylaminoazobenzene. They had previously shown that starvation and carbon tetrachloride poisoning does not prevent the activity of the liver slices. They point out that this is in striking contrast to the *in vivo* handling of estrogens which is extremely sensitive and impaired even by minor "subclinical" liver damage. They emphasize again the role of the excretory function of the liver which, in the intact animal, operates in addition to the metabolic inactivation of these substances.

György, Rose & Shipley (119) found that the estrogenic hormones, estrone, estradiol benzoate, and ethinyl estradiol, showed lipotropic activity when they were administered orally to rats being fed a diet conducive to fatty livers. The effect was small in male rats, but was enhanced considerably when the estrogen was administered with a small quantity of methionine. They suggest that the hormone may allow a more efficient use of methionine as a lipotropic agent. The effect cannot be due to the anabolic activity of estrogens, for testosterone with much greater anabolic activity has no such effect. Progesterone and desoxycorticosterone were also inactive.

A correlation between the occurrence of cirrhosis of the liver and primary carcinoma of the endometrium in women [Speert (120)] indicates that accumulation of estrogen, because of the failure of the damaged liver to metabolize it properly, may be a factor in the development of such cancers. On the other hand, Tagnon & Trunnell (121) found that the incidence of abnormal liver function tests was not strikingly different in patients with cancer of the breast from that found in a control group. Hence, although estrogens are effective in the production and growth of mouse mammary cancer, they are apparently not important in the production of human breast cancer.

In a study of the inactivation of testosterone propionate by the liver of the white rat *in vivo*, Grayhack & Scott (122) report that the mechanism persists even in face of apparently severe damage as a consequence of starvation, dietary deficiency, carbon tetrachloride, and in the hypophysectomized castrated adult male rat. Since similar treatments interfere seriously with the metabolism of estrogens, it would appear that these two sorts of hormones are handled differently, the testosterone being inactivated but not excreted by the liver.

Samuels *et al.* (123) found a difference in the enzyme systems responsible for the metabolism of testosterone by liver slices in cold blooded and warm blooded vertebrates. DPN and citrate were necessary in birds and mammals,

but not in fish, amphibians, and reptiles. They suggest that the occurrence of the system activated by DPN and citrate is related to the appearance of homeothermic mechanisms.

The rapid disappearance of gonadotropic hormones in the organism may be largely due to inactivation in the liver [Hall (124)]. Anterior lobes of rat pituitaries, implanted subcutaneously into immature female rats, produced increase in size of the ovaries compared to those transplanted intraperitoneally or into the spleen. Furthermore, incubation of chorionic gonadotropins with fresh rat liver homogenates resulted in a significant reduction in hormonal activity.

Successful autotransplants of the adrenal gland in the spleen and mesentery of the rat [Bernstein (125)] consisted entirely of adrenal cortical cells arranged in cords, but without distinct zonal pattern. The animals thrived and continued to grow and mature normally. This indicates that the liver plays no essential role in the metabolism of the adrenal cortical steroids. The fact that adrenal transplants atrophied if one adrenal was left in place indicates that accessory adrenal cortical tissue was not responsible for this growth and maintenance.

DIETARY INJURY—ACUTE MASSIVE NECROSIS

The puzzling conflict in the experience of various laboratories in the production of massive dietary cirrhosis in rats seems to have been explained by differences in tocopherol content of diets and also in the yeast that was used as a source of protein. György & Goldblatt (126) found that when they used a commercial vegetable fat (Crisco) they got no damage, but they did get it sometimes with lard, and especially with cod liver oil. They concluded that the tocopherol in Crisco served as a protection, but that the unsaturated fatty acids of lard and cod liver oil enhanced the damage because they put a strain on the metabolism of tocopherol. Schwarz (127) had independently shown that tocopherol deficiency might result in liver damage. Himsworth & Lindan (128) report that their successful diets were low in tocopherol as well as in methionine and cystine. The role of tocopherol has been corroborated by Abell & Beveridge (129). It seems clear, then, that this type of liver damage is due to the combined deficiency of the sulfur-containing amino acids and tocopherol.

György *et al.* (130) point out, however, that even the deficiency in both tocopherol and sulfur-containing amino acids fails to produce the effect consistently. They attempted to improve their diet by using yeast as a source of protein since this had been most successful in Himsworth's laboratory. The result was a failure with American yeast, but with British Baker's yeast, like that used by Himsworth, they report that for the first time massive necrosis has been observed as a truly regular occurrence in their laboratory. There is no tocopherol in either yeast, and no significant difference in content of sulfur-containing amino acids. They suggest that the action

of the British yeast might be due either to the presence of a toxic factor or to a low content of a special detoxifying constituent in the yeast.

Greenberg & Hoffbauer (131) produced acute massive necrosis in rats by the use of diets identical with György's, and made with British yeast. They investigated the excretion of coproporphyrin in the urine and feces, but found no significant increase during the course of their experiments. This, they believe, minimizes the likelihood of chemical or metal toxicity as the cause of the necrosis.

DIETARY INJURY—CIRRHOSIS

With the establishment of the etiology of acute hepatic necrosis, its distinction from dietary cirrhosis has become clearer. The latter is produced particularly on diets low in the lipotropic factor choline, and in methionine which may serve as a precursor of choline. In contrast with the acute necrosis, the fibrosis leading to cirrhosis occurs regularly when rats are placed on a proper diet.

That the fatty infiltration of the liver that precedes cirrhosis may be a necessary antecedent to the fibrosis has been emphasized by Glynn *et al.* (132). There is no extensive necrosis involved and the fibrosis is proportional to the degree of the preceding infiltration. Choline prevents both the fatty infiltration and the fibrosis. They point out that since a similar fibrosis occurs following other infiltrations, such as polyvinyl alcohols, cholesterol, kerosin, and glycogen, it seems to be independent of the nature of the infiltrating agent. The distention of the cells impedes the intralobular circulation which leads to malnutrition and atrophy of the parenchyma, particularly in the central part of the lobule. This injury leads to the fibrosis. This is similar to their explanation of carbon tetrachloride injury (133).

Hall & Drill (134), with different diets, have also produced extensive fatty infiltration, which eventually leads in long term experiments to diffuse progressive fibrosis, but with no antecedent necrosis. Rich *et al.* (135) have pointed out that any destruction of cells in livers of rats on cirrhosis-producing diets is so slight that it would easily be repaired in a normal liver, and suggest that an important factor in the development of cirrhosis is loss of regenerative capacity. In fatty livers of rats on a low protein, choline-free, high fat diet they found islands of fat-free cells, some of which were in mitotic activity. In the regeneration of such livers after partial hepatectomy, they found these fat-free cells to have 500 to 2,000 per cent more mitotic activity than the fat laden cells. This is in contrast to normal livers where cells in all regions participate in the regenerative process. They feel that this marked impairment of regenerative capacity in the fatty liver may play a significant role in the pathogenesis of cirrhosis. With the inhibition of normal regenerative replacement of dying liver cells by new ones, the alternative occurrence of fibrosis is favored.

The course of the development of the fibrosis has been a matter of considerable dispute, but it seems now to be settled by the studies of Hartroft

(136). The initial distribution is centrolobular. The idea that it might arise around the portal canals seems to have had its origin in the deceptive appearance of some multinucleate cells that resemble atypical bile ducts. These cells arise by the progressive confluence of fat laden liver cells. The boundary between separate cells breaks down and the fat droplets fuse until large fat-filled spaces are produced that are surrounded by a layer of cytoplasm. These he calls lipodiastaemata. They are much larger than the normal hepatic cell, and may contain as many as 80 nuclei. As fibrosis appears, they shrink. As the fat disappears, their walls thicken and the nuclei become distributed around the walls in such a way that, as long as the vacuole persists, they present the appearance of atypical bile ducts, and, in an area of fibrosis near a central vein, make it look as though the fibrosis had originated in a portal canal.

The prevention of cirrhosis involves the prevention of accumulation of fat and the maintenance of normal architecture and function of the liver. György & Goldblatt (137) have studied and discussed its cure. They worked with rats kept on cirrhosis-producing diets. The use of lipotropic factors was disappointing in very severe cirrhosis, and even in mild cases, improvement was obtained neither with complete regularity nor in a short time. In the most favorable cases they obtained reduction of fat infiltration, regeneration of hepatic parenchyma, and reduction of fibrosis. It does not follow, however, that anything that prevents cirrhosis will contribute to its cure, for thiouracil, which prevents cirrhosis, seems to be harmful, if anything, to its cure.

Hypothyroidism protects rats against the cirrhosis which usually results from ingestion of choline-deficient diets [Handler & Folliis (138) and György & Goldblatt (139)], but it actually augments the usual accumulation of liver lipids in choline-deficient rats [Handler (140)]. The hepatic necrosis of choline deficiency seems, then, to be dependent upon at least a normal level of thyroid activity, as well as upon the chronic fatty liver.

DEHEPATIZED RAT AND ISOLATED LIVER

In his Welch Lectures, Mann (141) has summarized physiological contributions that have been made with dehepatized animals. Ingle (142, 143) has described a technique by which eviscerated rats may be kept alive for as long as 48 hr. Prestrud *et al.* (144) studied the changes in carcass urea of such rats. After 24 hr. the total carcass plus urinary urea was lower than in the controls, and after 48 hr. still lower. There is no rise in the urea concentration of the body in the absence of the liver. They conclude that the results are indirect evidence for the occurrence of urea catabolism. Oberdisse and Hering (145) studied glycogen formation in the isolated liver of the dog when glucose was added to the perfusing blood. They found that addition of desoxycorticosterone acetate neither increased the production nor prevented its progressive decrease. The technique of Werthessen (146) for prolonged maintenance of whole organs in a perfusion pump should be profitably applied to such problems.

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PERIPHERAL CIRCULATION

BY KHALIL G. WAKIM

Section on Physiology, Mayo Clinic, Rochester, Minnesota

This review presents most of the contributions made to the literature on the peripheral circulation during the period July, 1949 and July, 1950. Occasional older references are included only for the purpose of clarifying certain points referred to by the authors. In addition to compilation of the facts presented, integration and critical evaluation were attempted where such were deemed helpful.

METHODS

Windfeld (1) found tetraethylammonium salts (TEA) a valuable supplement to the methods formerly used for the investigation of peripheral vascular diseases. He believes it diminishes dysbasia by release of vasospasm and reduces the pains of thromboangiitis obliterans and arteriosclerosis. Rahn (2) derived an equation which expresses the alveolar air concentration in terms of the relative alveolar ventilation and pulmonary blood flow. By a flexible catheter technique Haddy and associates (3) measured the pulmonary arterial and venous pressures in the anesthetized dog simultaneously with cardiac output, intrathoracic pressure, and systemic arterial and venous pressures. Jaques and associates (4) reported a method for determination of heparin in the blood, by which 80 to 90 per cent of the heparin added to the blood is recovered, while complete recovery of added heparin is obtained from plasma. Vanatta *et al.* (5) reported that after change of the bath and chemical treatment of the membrane, as well as attention to other details, nephrectomized dogs were maintained to the twentieth day and dogs otherwise deprived of renal excretory function were maintained for a month, at the end of which time they were killed for pathologic study. Salisbury (6) described what he considered a safe, effective, and easily controlled apparatus for cross transfusion. Obel & Schmiterl w (7) described a new electronic method for estimating arterial pressure in intact unanesthetized dogs. There was a close agreement between this method and the usual direct mercury manometer method.

Kety (8) presented a method for determining the clearance of radioactive sodium from its site of injection in a tissue and suggested that the clearance constant represents a valid and convenient measure of the local circulation in its broadest sense, and therefore a clinically useful determination. Wolff & Pochin (9) described a method for quantitatively estimating the vasodilator after-reactions occurring in recently cooled fingers. Cooper (10) said that the measurement of the rate of disappearance of radioactive saline solution from the muscles of the extremities, as determined by means of electromechanical apparatus, constitutes an accurate method for evaluation of effective blood flow in the extremities. Watkins (11) described a polythene tubing

cuvette which adapts the Millikan oximeter for measurement of oxygen saturation of drawn samples of whole blood. Bohr and associates (12) attacked the validity of the measurement of skin colorization time after injection of Evans blue as a test of the ability of rutin and other flavones to decrease capillary permeability. Increase in the skin colorization time could be roughly correlated with the ability of the individual flavone to depress arterial pressure, thereby decreasing peripheral capillary blood flow. Lund (13) described a condenser manometer for studying the circulation in the fingers and toes. He could record accurately the digital volume pulse even from part of the finger or toe in, for instance, only the terminal phalanx.

Saltzman & Rosenak (14) described a pump that conveys blood under sterile conditions without hemolysis for 72 circuits of the blood volume. It has no valves and contains no dead space. By use of the Burch-Winsor plethysmograph, Robertson and co-workers (15) described a simplified venous occlusion method of digital blood flow estimation. Dale (16) described a new apparatus which is inexpensive and simply applied at a one-stage operation for procurement of internal venous blood. It was well tolerated by dogs for a considerable period. Farrell & Anderson (17) described a device by means of which arterial pressure in the aorta of unanesthetized rats can be measured frequently over a long period. Brown (18) evaluated a new capillary resistometer, the petichiometer, by making determinations on 100 patients with the Dalldorf resistometer and vacuum gauge on one forearm and the petichiometer on the other. The advantages of the petichiometer are its simple use, its compactness, and small size. Richardson and associates (19) described an electromagnetic blood flow meter which can be used for a continuous permanent recording of mean blood flow. They find it adaptable to measure pulsatile blood flow in the respect that it readily records the effect of the heart rhythm and respiration on blood flow. Johnson *et al.* (20) found that when vein grafts were used to bridge defects in arterial walls, some dilatation occurred in the grafts, but there was no evidence of aneurysm formation. The graft walls progressively thickened by an increase of the fibrous tissue in all layers of the graft wall.

Kondo and associates (21) found that arterial occlusion proximal to the knee, by inflation of the cuff to a pressure of 300 mm. of mercury for 5 min., was suitable for demonstrating a state of vascular insufficiency in the foot or toe. Stenstrom (22) attempted procedures to direct arterial blood backward through the cardiac veins, but was uniformly unsuccessful. By use of a Sterling Automatic Pipette, Murray & Huston (23) prepared a very satisfactory pulsating perfusion apparatus. Petterson & Clemmedson (24) developed an instrument for recording arterial pressure by use of a mechanoelectronic transducer. Welch & Callow (25) presented and appraised the various current methods used in the treatment of portal hypertension. Fishback (26) described a new test for vasopressor substances in the blood of hypertensive subjects, depending on the injection of 3 cc. of human blood serum into the ear vein of rabbits and the subsequent determination of the animal's circula-

tion time by a fluorescein method. Seven and a half seconds circulation time for this was judged normal; longer than that, abnormal. Serum from hypertensives usually prolonged the circulation. This was attributed to the presence of excessive vasopressor substances in the serum from hypertensives. Ahlquist (27) described a method for the study of uterine blood flow and myometrial activity. Drugs have an important effect on uterine blood flow through both direct vascular and indirect myometrial action.

ARTERIAL PRESSURE

Peterson and associates (28) reported that in surgical patients marked hypotension may follow return from the lithotomy position to the horizontal position. In conditions of low arterial pressure primarily caused by vasodilatation, elevation of the legs acts as an autotransfusion and is of great help. From a study of a series of exercise tests on 1,000 Ceylonese subjects, aged 10 to 25 years and of both sexes, Cullumbine (29) concluded that the slower the resting pulse rate or the lower the resting systolic arterial pressure, the slower is the postexercise pulse rate or the lower is the postexercise systolic blood pressure, respectively. Dexter and associates (30) reported that the average mean arterial pulmonary pressure in man at rest was 15 mm. of mercury and the average mean "pulmonary capillary" pressure was 9 mm. of mercury. By means of the foot method described by Kersten and associates (31), Heymann & Salehar (32) measured the arterial pressure in unanesthetized, unheated rats. The arterial pressure increases with age and weight in the growing rat. Levy & Berne (33) noted that judicious compression of the pulmonary artery can reduce the output of the left ventricle significantly without causing a drastic fall in arterial pressure. Andersson and associates (34) stated that the causation of the Mayer waves in the arterial blood pressure is explained in terms of rhythmic excitation of the chemoreceptor mechanisms occurring in animals suffering from the effects of hemorrhage. Babkin & Kite (35) reported rhythmic variations in arterial pressure of dogs with different amplitudes and durations caused by different factors.

Rodbard and associates (36, 37) reported that an increase or decrease in body temperature of the turtle results in covariance of the systemic arterial pressure. Lehmann & Reinecke (38) observed that higher uniform pressures within the infrasystolic range applied over the length of the tail of the mouse by a pneumatic sheath caused progressively more necrosis of the distal end. Barger and co-workers (39) noted that the elevation of venous pressure was related to work intensity and also to the total amount of work done. In severe exercise, as exhaustion approaches, the cutaneous vessels constrict markedly. Thomson & Doupe (40) demonstrated that the use of narrow cuffs gave high systolic and diastolic auscultatory readings. This is so because a narrow segment of compression will offer less resistance to a pulse wave than will a wide one. De Molina and associates (41) excluded the liver in dogs for one hour by portajugular shunting or by clamping the portal vein and the hepatic artery singly or simultaneously and obtained no modification of the ar-

terial pressure, nor of the vagal pressor reflex, nor of the depressor effect on stimulation of the carotid sinus. Reinstatement of the hepatic blood flow into the main circulation after one hour of exclusion caused no change in the arterial pressure nor in the previously mentioned pressor or depressor reflexes. They concluded that their findings do not confirm the concept of Shorr and collaborators that the liver is the organ which forms vasoactive depressor material when this organ is under anaerobic conditions.

Neil and associates (42, 43) reported that the carotid sinus nerve does not contain pressor fibers and that the pressor response to electrical stimulation of the carotid sinus nerve is due to excitation of the chemoceptor afferents contained in the nerve. They presented data showing that the effects on arterial pressure of electrical stimulation of the aortic nerves are dependent on the type of anesthesia employed. Lagerlöf & Werkö (44) recorded the pressure in the small branches of the pulmonary artery obstructed by a heart catheter, and called the obtained pulse the pulmonary capillary venous pressure pulse. This pressure is about 2 mm. of mercury higher than the left atrial mean pressure. In left ventricular failure, the pulmonary capillary venous pressure and hence the capillary pressure may be elevated above the colloid osmotic pressure of the plasma. Kinmonth and associates (45) reported evidence indicating that the caliber of the large arteries follows passively the systemic blood pressure; it increases with rises in arterial pressure and decreases with falls in arterial pressure, however these are produced. Dow and associates (46) measured with Hamilton and saline manometers the pressure in pulmonary artery and pulmonary capillaries. Blood flow through the lung was determined by the direct Fick principle. Pulmonary arteriolar resistance was determined by Poiseuille's equation. Segall and associates (47) studied carotid sinus pressure on the right and left sides alternately in 446 patients and failed to induce cardiac pain.

In a study of man's reactions to the effects of gravity produced by tilting erect to 70° from the supine position or by exposure to positive acceleration (centrifugal force), Brown and associates (48) noted a fall in arterial pressure and increase in heart rate. Vakil (49) presented an interesting article on the history of the study and development of the concept of the pulse and circulation. Elbel & Holmer (50) established in healthy male subjects pulse rates in the recumbent position prior to exercise, and at uniform intervals following exercise until the pulse rate had returned to the pre-exercise level. The deceleration in pulse rate following exercise was rapid, and the mean recovery time was 27 minutes. Alexander (51) suggested that his observations reinforce the concept that the femoral arterial pulse contains a prominent pressure oscillation due to a standing wave created in the central aortic system. He (52) stated that there is nothing unusual about the peripheral pulse pressures in aortic insufficiency; the large values observed are merely a consequence of the large central pulse pressure together with the relative augmentation of this pulse pressure that is observed in normal peripheral pulses.

HYPERTENSION

Andreassian (53) found that in the treatment of hypertension bismuth gave entirely satisfactory results by reducing the pressure, relieving the headache and vertigo, and permitting the patient to follow a normal life. Werkö & Lagerlöf (54) made a study of the cardiac output, right atrial, right ventricular, pulmonary and brachial arterial pressures in patients with compensated hypertensive cardiovascular disease and in those with signs of right or left ventricular failure. The cardiac output was within normal limits in all compensated patients. The pressure in the right atrium was increased only in the case with right ventricular failure. De Takáts (55) brought out evidence from experimental data and clinical observations that corticoadrenal activity is a factor in at least some cases of hypertension. Grollman & Halpert (56) noted that the development of hypertension is dependent on the status of the kidneys at the time of removal of the first kidney. If lesions are present, hypertension develops; if absent or minimal, the animals remain normotensive. Perera & Pines (57) observed in patients with hypertensive vascular disease that simultaneous administration of an adrenocortical extract appears to block the pressor effect of desoxycorticosterone acetate when used alone. Koenig & Koenig (58) reported that during ammonium intoxication a considerable hypertension occurs, but hypertension does not play an important role in the genesis of ammonium lung edema. Cicardo (59) considered the sympathetic nervous system, the adrenals, and the hypophysis as the causative factors of the hypertension which follows intracranial or diencephalic injections of potassium chloride in dogs.

Wakerlin (60) stated that more work is needed for solving the enigma of essential hypertension. The cause, pathogenesis, and pathophysiology are to be determined, following which, treatment will become rational, specific, and more effective. Hall & Hall (61) reported that hypertension produced in rats by administration of desoxycorticosterone acetate continues to increase following total nephrectomy and is not dependent on renal mechanisms nor is it a consequence of renal vascular damage. Edwards and associates (62) stated that in patients in whom coarctation of the aorta and patent ductus arteriosus coexisted, changes of significant proportions involved the intrapulmonary arteries and arterioles. Herring (63) reported general agreement that the immediate mechanism of essential hypertension is arteriolar spasm, regardless of whether the pathogenic factors are neurogenic, humoral, or renal, and that best results in the control of the disease and prolongation of life are attained by relieving the spasm. Reyersbach & Butler (64) presented six case histories of children with hypertension which suggested no general conclusions concerning the benefit that can be expected from sympathectomy in individual children with essential hypertension or hypertension associated with demonstrable renal disease. Spatt & Rosenblatt (65) reported that the incidence of hypertension in patients with portal cirrhosis is significantly lower than in the general population. Derome (66) called the hypertensive a

"fragile package" in which, with care and encouragement, the precipitation of cardiac failure, paralysis, and other accidents can be retarded.

Muirhead *et al.* (67) reported the development of hypertensive cardiovascular disease in bilaterally nephrectomized dogs which were kept in a relatively good state of health for a sufficiently long time. From the use of several pressor-depressor tests, Postelli & Palmer (68) concluded that in most patients with essential hypertension the arterial pressure is quite variable, but that the variability is a doubtful guide to prognosis and the selection of patients for medical or surgical treatment. Davis and associates (69) attempted to produce low-grade hepatic pathologic changes by partially clamping the portal vein and hepatic artery to inhibit the formation of hypertensinogen by the liver and thereby relieve the experimentally produced hypertension. Heller (70) stated that high systolic pressure is of less importance than diastolic high pressure. Birchard (71) summed up his remarks by stating that some day we shall know whether the cause of hypertension is renal, adrenal, nervous, or hepatic and whether the prime outside cause is diabetes, infection, or heredity. Assali (72) summarized the new pharmacologic tools which have been developed in the physiologic study of hypertensive diseases of pregnancy. Hilden (73) determined urea and diodrast clearances in essential hypertensives before, 10 days after and 12 to 18 months after sympathectomy. Diodrast clearance was a little increased, but urea clearance was unchanged 10 days after the operation. From 21 patients with hypertension, Mylon & Freedman (74) extracted renin free of hypertensinase from one patient in moderate amounts and from three in slight amounts, while 17 gave negative results.

Friedman & Friedman (75) found that, after treatment with desoxycorticosterone acetate and saline solution was discontinued, four of seven rats maintained a "self-sustaining" hypertension. Cornwell (76) presented a case of hypertension due to partial occlusion of the right renal artery, with cure of the hypertension by nephrectomy. Stamler and associates (77) reported that serial renal clearances on nephrogenic hypertensive dogs revealed no tendency for renal function to become progressively impaired. Smithwick (78) expressed the opinion that the beneficial effect of splanchnicectomy on the course of hypertensive cardiovascular disease is not due solely to the effect on basal blood pressure levels but is the result of a combination of effects. Surgical treatment has materially and significantly improved the prognosis for hypertensive patients. Stamler *et al.* (79) observed that in both nephrogenically and spontaneously hypertensive dogs the local parenteral injections of turpentine or carbon tetrachloride, or the subcutaneous implantation of renal tissue produced an abscess and caused a sustained fall in arterial pressure and an increase in renal blood flow. Stock & Schroeder (80) found that blood from hypertensive patients contains pressor substances with prolonged action, possibly amines, which are not present in most normal persons. Chisholm (81) stated that there is considerable variation in the response of hypertension to treatment. The good results obtained by differ-

ent treatments are obtained because the causes of essential hypertension are varied.

Evans (82) suggested that there is no single or primary cause of hypertension. Primary causes may be neurogenic with resulting changes in renal circulation or endocrine disorder. Barnett (83) reported that since norepinephrine appears to be a universal vasoconstrictor and produces a rise in the systolic and diastolic arterial pressures with no change in cardiac output, it may possibly be the agent concerned in human essential hypertension. Wilkins (84) found *veratrum viride* to be effective in moderating the arterial pressure in essential hypertension; however, it is far from being an ideal or curative agent in this condition. Frant & Groen (85) found that the condition of the fundus of the eye is a better guide for the prognosis of hypertension than the increase in arterial pressure. Blacket and associates (86), with continuous infusion of renin for about 18 days, produced a maintained hypertension in rabbits. Equal increments in doses of renin produced progressively smaller increments in the degree of hypertension. They concluded that hypertension following renal arterial constriction is due to the release of renin.

BLOOD FLOW

Aas & Blegen (87) found that the renal blood flow was pronouncedly reduced, but the glomerular filtration rate was usually reduced to lesser degree in heart failure. The renal blood flow was reduced in anemia but increased in hyperthyroidism. Clinical improvement of either condition led to normal values in renal blood flow. In a study of the relation between blood flow and blood pH in an active muscle, Gollwitzer-Meier (88) showed conclusively that the blood pH is not the sole or even the main factor responsible for the vascular reactions occurring in a muscle during and after muscular activity. Winsor & Ottoman (89) reported that intravenous injection of 50 mg. of 2-benzyl-4,5-imidazoline (priscol) caused, in normal subjects, an average increase in volume in occluded fingers from the control value of 10.6 to 13.6 cu. mm. per 5 cc. of tissue per sec. and in toes, from 2.8 to 6.5 cu. mm. per 5 cc. of tissue per sec. The temperature changes also showed an increase in peripheral blood flow. Atropine did not prevent the action of priscol. Cheng (90) could not confirm the claim made by Engel (91) that lumbosacral sympathectomy gives a reduction in dye secretion into the knee joint, despite increased muscle temperature and presumably increased blood flow. Only severe vascular obstruction in the limb influences dye excretion in the knee joint, probably because of decreased capillary pressure. Hoobler and associates (92) reported that in doses of 500 mg. given intravenously, tetraethylammonium chloride produced an average of sevenfold increase in foot blood flow, a fourfold increase in hand blood flow, and slight increase in forearm and calf blood flows in normal subjects.

Franklin and associates (93) reported that acute anoxia, in sufficient degree, produces a marked diversion of the renal cortical blood flow in the innervated but not in the denervated kidney. Hollander & Horvath (94)

suggested that determination of joint temperature may prove to be a means of measuring the efficiency of circulation in the synovial membrane. They reported that changes in joint circulation do not parallel those in skin but frequently are directly opposite. Kottke and co-workers (95) noted that heat applied to the back by means of short-wave or microwave diathermy resulted in a significant reduction in renal plasma flow and glomerular filtration rate without significant changes in arterial pressure. They stated that diathermy heating reduces renal blood flow. Hayes and associates (96) reported that dihydroergocornine administered intravenously in total doses up to 0.4 mg. produced an average increase in blood flow of 94 per cent in the upper and 64 per cent in the lower extremities of human subjects. Maluf (97) stated that intra-aortic injections of India ink during life show that there is a normal intraglomerular and peritubular circulation during anuria or oliguria of the renal shutdown which follows intravenous injection of lysed erythrocytes during dehydration or shock. Gersten and associates (98) noted that mecholyl ion transfer caused cardiac acceleration and increased the blood flow of the treated extremity. Atropine produced a significant slowing of the heart when injected intravenously five minutes before ion transfer and had an inhibitory action on the increment in blood flow produced by mecholyl.

Grayson (99) stated that the response of the skin circulation to rising environmental temperatures consists of an increase in skin blood flow as the environment warms up. By external drainage of intestinal lymph in the rat, Mann and associates (100) obtained marked hypoprothrombinemia within twenty-four hours. Administration of adequate amounts of vitamin K led to normal level of prothrombin despite loss of lymph and even of a considerable quantity of blood as well. Stein *et al.* (101) made plethysmographic studies of blood flow in sympathectomized human limbs under the influence of varying doses of epinephrine injected into the femoral artery and showed that sensitization of muscle circulation is established and is greater for the dilator than for the constrictor mechanism. In a study of the effects of lumbar sympathectomy on the peripheral circulation of the hind limbs, Deterling & Essex (102) obtained significant rises of distal cutaneous temperatures and arterial flow and noted that a decrease in peripheral arterial pressure followed preganglionic denervation. Lee (103) observed the mesenteric and serosal capillary bed of guinea pigs under local anesthesia and noted that the "flight response" was frequently characterized by intense vasoconstriction of arterioles, complete stagnation of capillary blood flow, and a drainage of residual capillary blood into patent venules. Armitage & Arnott (104) explained the unexpectedly large volume of oxygen absorbed during deep breathing on the basis of the entry into the pulmonary capillaries of blood additional to the resting flow.

Rapaport and associates (105) suggested that the regulation of blood flow to the extremities at low ambient temperature is primarily determined by the thermal state of the body as a whole. By direct observation and

cinema recordings, Bigelow and associates (106) noted cessation of flow in the smaller vessels after local trauma to the region. The erythrocytes became packed into dark red homogeneous masses. This phenomenon was described as vascular stasis. Grayson (107) measured by thermoelectric methods the temperature of the wall of the exposed bowel following colostomy or ileostomy in human subjects and noted that spontaneous vasoconstriction in the skin of the extremities is accompanied by a spontaneous increase in the temperature at the site of colostomy. Barcroft & Dornhorst (108) described a plethysmograph for measuring blood flow through the human calf during rhythmic contraction of the gastrocnemius and soleus, and reported that the mechanical hindrance of the contractions reduced the flow to 40 per cent of what it would otherwise have been. Glaser (109) noted that on entering a warm room the forehead temperature of all subjects except one rose up to 1.7°C. above the rectal temperature. During warming, the rectal temperature always remained 0.4 to 1.2°C. below its initial level. Goetz & Ames (110) reported that immersion of one upper extremity or of both feet in water at 45°C. for 30 minutes, with prevention of the dissipation of heat from the body, normally results in reflex dilatation in the other extremities.

Greenblatt *et al.* (111) observed a complete cessation of the pain from peripheral vascular disease in thirteen instances after the patients had received a course of histamine in a retarding menstruum, and a higher and more prolonged rise in skin temperature of the lower extremities when results of treatment with histamine were compared with those of paravertebral block. Radigan & Robinson (112) found that in a cool environment (21°C.) the mean renal plasma flow of resting men was 685 cc. per minute and dropped 42 per cent during exercise in the same environment. Following local application of short-wave diathermy, Flax and associates (113) obtained four types of general responses in peripheral blood flow: no vasodilatation in the distal area; gradual vasoconstriction; marked vasodilatation; no change in blood flow during application of diathermy with an increase occurring later. Fetcher and associates (114) supported the validity of skin temperature as a measure of blood flow in the extremities under certain conditions only. If skin temperature is used for blood flow determination, the part of the body under investigation must lose heat at a rate of more than about 240 kcal. per sq. m. per hr. for good correspondence between blood flow and skin temperature changes. Durant and associates (115) found that air experimentally introduced into the coronary circulation, either directly or by injection into the pulmonary vein or left atrium, produces ischemia of the myocardium in areas supplied by involved vessels. Feucht and associates (116) reported augmentation of the rate of blood flow through the extremities of anesthetized dogs when sufficient hyperthermia was produced by hot moist packs.

Coulter & Pappenheimer (117) described the development of turbulence in bovine blood flowing through medium bore glass tubes and concluded that anomalous flow of blood is not restricted to capillary tubes, but can be de-

tected with refined methods in large tubes at low rates of shear. Langohr and associates (118) noted that a sharp reduction in lymph flow from a burned foot occurs during the entire period of immersion in a cold bath, regardless of whether cold is applied immediately after the burn or some time later. The rise in protein concentration of lymph and in rate of edema formation is also retarded. Rosenfeld and associates (119) produced experimental frostbite by immersing a dog's feet in a liquid mixture of ethyl alcohol and solid carbon dioxide, and noted that the blood flow progressively decreases in proportion to the severity of injury during the period of freezing. The blood flow to the injured extremity increases only after thawing begins. Cold retarded lymph flow, protein concentration and edema formation, while warmth increased lymph flow and protein concentration in the treated foot. Ficarra (120) emphasized that adequate circulation in the serosal arterioles on the antimesenteric border of the small bowel indicates viability of the bowel even in the presence of discoloration, edema, and inhibition of peristalsis.

The most peripheral lymphatic vessels of rats, mice, and guinea pigs were found by Smith (121) to possess spontaneous intermittent contractility. The rate of contraction was shown to be directly proportional to the rate of formation of lymph, and contractions were apparently initiated by an increase in intraluminal pressure. The frequency of valves in lymphatic vessels, the distensibility of the lymphatics and their ability to return to normal caliber against an increased gradient of pressure are considered to be the essential elements of an intrinsic mechanism contributing to the transport of lymph. Barcroft & Konzett (122) compared the actions of norepinephrine, of isopropyl-norepinephrine and of epinephrine on the blood flow in the forearm and calf and on the heart rate and arterial pressure in unanesthetized man. Horwitz and associates (123) reported that heat invariably increased cutaneous blood flow selectively; the cardiac output per minute increased only slightly; arterial pressure, pulse rate, and metabolic rate changed little. Heat, alcohol, moderate doses of priscrol, and food caused selective vasodilatation of the skin of fingers and toes in varying degrees. Cooper *et al.* (124) assessed the blood flow through the hands of healthy subjects by the venous occlusion, plethysmograph, arterial inflow, by the hand calorimeter (heat elimination) and surface thermocouple (skin temperature). The methods were compared by using them simultaneously in pairs on the two hands.

Gilje (125) wrote a monograph discussing the major problems in the etiology, pathogenesis, and therapy of ulcer cruris. He gave a detailed review of the hypotheses concerned with the formation of "varicose" or "stasis" ulcers. Evaluation of the data obtained from skin temperature measurements, capillary microscopy, and histamine pricks did not indicate that local arterial circulatory disturbances are responsible for the development of the ulcers.

Weisman & Allen (126) reported that an intravenous injection of 500 mg. of vitamin C, followed after an interval by an intramuscular injection of 5 cc. of 4 per cent aqueous solution of histidine monohydrochloride and a subcutaneous injection of 100 mg. of vitamin C did not cause an increase in digital blood flow as measured by changes in the temperature of the skin. By use of digital plethysmography and skin temperature readings, Goetz (127) investigated the effect of posture on the peripheral blood flow. He noted that even slight changes in posture have marked effect on the plethysmographic appearances. In the erect posture, the height of the pulse volume is only a fraction of that recorded in the elevated limb. In his opinion, digital plethysmography is superior to skin temperature in assessing the state of the peripheral circulation. Mendlowitz & Abel (128) compared the blood flow in the human toe, determined calorimetrically in normal persons and in patients with residual symptoms of trench foot and frostbite. The significantly decreased blood flow in the latter group was attributed to organic obstruction or constriction of the small arteries of the foot. Richardson and associates (129) suggested that irradiation by short-wave diathermy may or may not increase the flow of blood in the area, depending on the degree of tissue hyperthermia. Similarly with microwaves, the flow of blood in the irradiated area may or may not increase, depending on the magnitude of tissue heating.

Swigart and associates (130) found the arterial supply of the three divisions of the esophagus to be segmental in nature; its scheme resembles the segmental pattern of arteries sent to the gut prior to growth, rotation, and peritoneal fixation. There are ascending and descending branches of esophageal vessels which course along the anterolateral or posterolateral aspects.

Seely & Gregg (131) cannulated the pulmonary artery in dogs and obtained by the rotameter blood flows ranging from 40 to 100 cc. per kg. Lee & Holze (132) visualized the bulbar conjunctival capillary bed in man with the microscope at a relatively high magnification. The arrangements of the vessel elements, the velocity of the blood flow, and the nature of spontaneous vasomotor activity in the conjunctival vessels of man are similar to those observed in lower animals.

By use of an ergograph for exercise and a plethysmograph for blood flow, Shepherd (133) observed that in patients with arteriosclerosis and claudication the calf blood flows failed to reach their maximum after exercise until an average of about six minutes had elapsed. Krogh (134) stated that in resting muscles the average diameters of capillaries are very small and the erythrocytes must undergo considerable deformation in the passage. Roofe and associates (135) found that peripheral blood has a significantly greater number of both erythrocytes and leukocytes than heart blood.

By intravenous injection of radioactive sodium, Wright and associates (136) studied the rate of venous blood flow in the legs of pregnant women. An increase in the foot-groin flow time, which became greater with the advance of pregnancy, was observed. A marked increase in the foot-groin flow

time occurred during labor, followed by rapid return to normal after delivery. Comparison of arm and of leg flow rates showed that the flow rates in the upper limb underwent no significant change.

Murphy and associates (137) made a comparative study of the effect of priscoline, papaverine, and nicotinic acid on the blood flow in the lower extremities of normal people. Priscoline was found most effective in increasing the blood flow through portions of the normal lower extremity that are predominantly composed of skin and subcutaneous tissues.

Horvath and associates (138) reported inconstancy of the temperature of the blood throughout the vascular system. The temperature at any point was considered dependent on the relative metabolic level of the tissues through which it passes and the temperature of the blood with which it mixes. Sherlock and co-workers (139) determined the estimated splanchnic blood flow (E.S.B.F.) by the sulfobromophthalein extraction technique, using hepatic vein catheterization. The results suggest that, unless extrahepatic removal mechanisms for sulfobromophthalein are saturated, the values for E.S.B.F. are falsely high. With adequate peripheral sulfobromophthalein levels, only small fluctuations in E.S.B.F. occur.

Brigden and associates (140) noted that tipping of normal subjects from supine to erect posture caused a decrease in right atrial pressure, cardiac output, and forearm blood flow. The decrease in forearm flow did not occur in sympathectomized forearms. In patients with left heart failure, Brigden & Sharpey-Schafer (141) found the forearm flow was greater in the "feet down" position than in the "feet up" position, a reversal of the findings in normal subjects and in patients similar except for the absence of left heart failure. When the nerves were blocked by procaine hydrochloride, there was no change in flow of blood with postural change. Mendlowitz (142) tested and critically examined the calorimeter method for measuring digital flow and found the over-all maximal error to be small. Lynn & Barcroft (143) obtained a great increase in blood flow in normal and abnormal feet after lumbar sympathectomy. Krusen and associates (144) obtained significant increase in skin temperature and blood flow in the extremities after application of hot packs for 15, 30, and 45 minutes. Unilateral application of hot packs to the extremities produced insignificant increases of blood flow in the contralateral extremities. Burchell and co-workers (145) reported two cases of coarctation of the aorta with associated hypotension in the left arm. The flow of blood was consistently greater in the right than in the left arm.

Engel and associates (146) obtained significant increases in peripheral blood flow in the extremities when these were treated by contrast baths at water temperatures of 110°F. and 60°F. (43.3°C. and 15.6°C.) beginning with an initial period of 10 minutes immersion in the hot water, alternating in the hot and cold water every one and four minutes respectively, and ending with the hot water, making altogether a total of 30 minutes. Burt (147) reported an increased forearm blood flow and a tendency to muscular and cutaneous vasodilatation in the upper limbs during the later months of pregnancy.

VASOMOTOR MECHANISMS

Goetz & Katz (148) noted that dihydroergocornine had adrenolytic properties, being able to suppress or reverse the pressor effect of epinephrine injected into man. Because it has both sympatholytic and adrenolytic activity, it may be useful in the treatment of disorders involving abnormal activity of the sympathetic nervous system. Steinberg (149) suggested that, in the presence of vasospasm in properly selected cases, tetraethylammonium should be helpful, especially if the vasospasm is of brief duration, but in patients whose vascular diseases are of long duration, this drug is of questionable value. Middleton and associates (150) reported that, in the isolated perfused mammalian heart, stimulation of either the vagus or sympathetic nerve leads to release of easily detectable amounts of a substance with epinephrine-like properties. This suggested the existence in the heart of adrenergic ganglia connected with the vagus.

Hoobler and associates (151) produced blockage of sympathetic vasomotor nerves in man by means of spinal anesthesia, caudal anesthesia, and lumbar paravertebral block or within twenty-four hours after sympathectomy. Secker (152) noted that the vasomotor response to central sciatic stimulation in the cat steadily declined in intensity and could be extinguished with repeated stimulation following acute adrenalectomy. Intravenous administration of an active extract of the adrenal cortex restored the response to normal or nearly normal. Armitage & Knott (153) found that the oxygen uptake in the horizontal position was approximately one third of that in the upright position. Stein and associates (154) noted the development of an increased sensitivity of blood vessels to epinephrine after the usual type of lumbar sympathectomy in man. The sensitization of muscle circulation to dilator doses of epinephrine was much more marked than to constrictor doses. Hill and associates (155) stated that tetraethylammonium is of definite value in preventing ischemic gangrene, muscular weakness, and subsequent paralysis produced when the aorta is ligated and divided just above the bifurcation. By use of the optical digital plethysmograph, the peripheral vasodilatation effect produced by pentamethonium iodide was studied by Arnold and associates (156). They found that vasodilatation begins in normal people within a minute after injection and persists for at least one hour. Binet & Burstein (157) reported that peripheral vasoconstriction originating from the central mechanism may be accompanied by carotid hypertension, caused by anoxemia, hypercapnia, carotid occlusion, or excitation from the proximal ending of a vagus nerve or by hypotension due to hemorrhage, embolism, or injection of histamine.

Dey and associates (158) noted that the coronary blood flow was regularly and markedly augmented during simulated emotional excitement. They suggested that emotional precipitation of anginal attacks is not due to absolute reduction in coronary blood flow, but to structurally altered coronary vessels which are unable to distribute efficiently the augmented flow, with the result that the increase relative to the augmented demand of the

heart during excitement is insufficient. Last and associates (159) have shown that both dibenamine and SY-28 were absorbed by the intact rabbit skin and blocked the vasoconstriction produced by intracutaneously administered epinephrine. Both these blocking compounds were fixed locally in the skin. Marzoni and associates (160) produced by prisco, by etamon, and by dibenamine a blocking of reflexes normally dependent on the sympathetic nervous system.

By prior administration of the adrenergic blocking agents, MacKay and associates (161) completely prevented the acute pulmonary edema which follows the administration of ammonium salts to guinea pigs. Ammonium salts cause a striking hyperglycemia which is not directly related to the edema formation. Graham & Douglas (162) produced arterial hypotension in dogs and cats by bleeding or by high spinal anesthesia and studied the effects of 18° head down position on the cardiac output and arterial pressure. There was no significant improvement in cardiac output or arterial pressure in hemorrhagic hypotension, but a significant increase in arterial pressure followed the adoption of the 18° head down tilt in the hypotension of high spinal anesthesia. In an attempt to demonstrate the presence of pressor substances in the blood, Page and associates (163) repeatedly cross-circulated heparinized blood between dogs with various organs removed. These "indicator" animals were made highly sensitive by bilateral nephrectomy, spinal cord destruction, and carotid sinus inactivation. The removal of the liver, kidneys, spleen, and adrenals, followed by cross-circulation with indicator dogs, showed that none of these organs is exclusively responsible for the appearance of pressor substances in the blood. Page (164) suggested that the liver participates in the mechanism concerned with the control of the responsiveness of the cardiovascular system to vasoactive substances. Hershey & Zweifach (165) found cyclopropane to exert little influence, pentothal an intermediate effect, and ether a drastically unfavorable effect on the specific homeostatic mechanisms regulating the peripheral vascular bed.

Eckenhoff (166) presented a résumé on the physiology of the coronary circulation and supportive evidence for the thesis of regulation of coronary blood flow by the metabolic demands of the heart. Data on vasopressor and cardiac drugs that facilitate coronary flow were also presented. Grayson & Swan (167) obtained an index of blood-flow change in the human colon from the changes in temperature of the portion exposed at colostomy. McDowall (168) observed that the vessels of the muscles are not particularly sensitive to depressor reflexes. In spite of the fact that they may be caused to dilate by injected epinephrine or norepinephrine, they are tonically constricted by fibers of the lumbar sympathetic cord. Page & Taylor (169) reported that blockage of the sympathetic ganglia and the carotid sinus mechanism by tetraethylammonium chloride in large doses greatly increases responses to many vasoactive drugs. Blacket and associates (170) suggested that the failure of hypertension to be maintained during, and the profound fall of pres-

sure after, a prolonged infusion of norepinephrine or epinephrine are due to release of vasodilator substances into the circulation. Brun (171) stated that the vasoconstrictor substance in the serum or extravasated blood is probably the strongest constrictor agent of pial arteries so far discovered.

Lynn & Barcroft (172) reported much increase in blood flow in the feet with normal arteries after sympathectomy, reaching a maximum on the second day. Also, in feet with abnormal arteries, the blood flow increased after sympathectomy and returned to about double the normal. Lynn & Martin (173) found that vascular tone of the feet had not returned at the end of four months after lumbar sympathectomy. Hegnauer and associates (174) reported that in the early stages of hypothermia, the pulse rate reflects the algebraic sum of reflex excitatory and cold depressor influences. Inadequate coronary flow and reduced metabolic rate are the cause of death. Lange and co-workers (175) investigated the behavior of the circulation under the influence of experimentally induced acidosis and noted a reduction in peripheral resistance and in the pulse rate and an increase in cardiac output. Katz (176) discussed the various factors concerned in the control of the coronary circulation.

CIRCULATION TIME

Kreyberg & Hanssen (177) suggested that the increased staining of the tissues in the area of application of mustard gas to the skin, which occurs within a few minutes after application of the gas, is caused partly by an increased circulation in, and partly by an increased permeability of, the minute vessels. In the course of a few hours the vessels became occluded and finally the blood flow stopped in the entire region. Lind (178) found that the circulation time bears a closer correlation to the weight than to the height, and that there is a tendency toward an increase with increasing age. Borden and associates (179) noted that in patients with mitral stenosis associated with pulmonary hypertension and in those with left ventricular failure, the same mean circulation was prolonged, and the cardiac output was reduced as compared with normal subjects. Ebert and associates (180) reported that by injection of T1824 into the pulmonary artery and measurement of the concentration of the dye in consecutive samples of blood obtained from the femoral artery, the mean circulation time from the pulmonary artery to the femoral artery was determined to be 10.2 ± 1.6 sec. in normal subjects. Lian and associates (181) stated that the most recommendable technique for measuring the circulation time is the arm-to-tongue method with decholin. It is most sensitive in detecting pulmonary capillary stasis. For exploration of capillary stasis in the greater and lesser circulations, the use of fluorescein is the best.

Gray & Paton (182) measured the circulation times in the greater and lesser circulations in the cat by recording the time interval between the beginning of a rapid injection of salt solution into one vessel and the moment of maximal conductivity change in another. Sutton and associates (183) re-

marked that the findings obtained from serial samples of right ventricular blood taken during the course of a steady injection of tagged erythrocytes into the main pulmonary artery of man indicated that detectable complete circulation occurred by the seventh to ninth second. Levi & Lewison (184) determined the segmental linear venous velocity by the use of radiosodium and found it to be 3.8 ± 0.3 cm per sec. from ankle to groin.

BLOOD VOLUME

Terzioğlu (185) attributed the increase in the total volume of blood, as well as in the erythrocytes, in rabbits injected with a hypertonic glucose solution, to the changes brought about in the acid-base equilibrium of blood. Grant (186) produced and maintained artificial closed pneumothorax in unanesthetized dogs for periods of 11 to 75 days by repeated insufflations of room air. In a few days the hematocrit, oxygen capacity, and erythrocyte count values rose above those of the control period and reached a maximum in two to four weeks. Frazer (187) presented a complete technique with precautions for the determination of the circulating blood volume. It is a correlation and compilation of several techniques with a unique calibration method added to it. Mills (188) noted that accumulation of blood in the legs increases the vital capacity by 0.25 to 0.5 l. Kjellberg and associates (189) reported that athletically trained persons showed considerably higher amounts of hemoglobin and blood volumes than other persons. The best trained men deviated by 41 per cent and the women by 44 per cent from the reference material. The amount of hemoglobin and blood volume may vary with the degree of physical training. They (190) found a clear correlation between the amount of hemoglobin and the pulse rate during rest. In certain persons, the heart volume diminished only slightly to a pulse rate of about 150 per minute, but afterward more rapidly.

Allbritten and associates (191) noted decreased blood volume in 10 patients with pulmonary tuberculosis admitted to the surgical service. By injecting P^{32} into an arm vein and taking blood samples at about three-second intervals from the artery of the opposite arm, Nylin & Celander (192) developed a formula for estimating the cardiac output from the curve obtained from drawing the concentration of indicator of the obtained samples as a function of time. According to the measurements obtained, 29 to 35 per cent of the total blood volume is contained in the heart and lungs. Mann & Guest (193) noted a rise in blood volume one hour after anesthesia and operation in most patients receiving seconal, morphine, and scopolamine premedication with spinal pentocaine-ephedrine anesthesia. Lyon and associates (194) believe that following blood loss, the mechanisms for the preservation or restoration of the total blood volume appear dependent on a state of positive fluid balance. When depleted through either operative or postoperative blood loss, the erythrocyte volume shows little tendency to recover spontaneously within the first 10 days following operation. In adequately hydrated

patients, serial determinations of the basal hematocrit offer the most useful index of uncompensated blood loss.

VENOUS SYSTEM

By transillumination, Seneviratne (195) made in frogs, mice, and rats a detailed study of the circulation in the intact liver and its reaction to various stimuli. He found the sinusoids thin-walled collapsible tubes with complete linings. Arteriovenous anastomoses were frequent. Irregular intermittent rhythmicity was observed in the hepatic circulation under normal conditions. Blood flow is under sympathetic control, but there is no evidence of parasympathetic supply. Ripstein (196) stated that esophageal varices are a manifestation of portal hypertension, and the most rational treatment of the problem is the establishment of adequate collateral anastomosis between the portal and caval venous systems. This is best done by a splenorenal end-to-end anastomosis, removing the spleen and preserving the function of the left kidney. Stone & Miller (197) found intramuscularly injected radioactive sodium can be quantitatively recovered from femoral vein blood if the collateral venous system of the upper part of the thigh is occluded. Lord (198) described several operative procedures which have effected significant improvement in patients suffering from the complications of hepatic cirrhosis and Banti's syndrome. Davis and associates (199) produced low-grade hepatic pathologic changes to inhibit the formation of hypertensinogen, and relieve experimentally produced hypertension. Reduction in blood flow to the liver is followed by a substantial reduction in the systolic arterial pressure in animals made hypertensive by the Goldblatt technique.

Swan (200) developed a venous shunt in dogs between the pulmonary vein and the superior vena cava by means of an end-to-end anastomosis of the azygos and pulmonary veins using a vitallium tube. He also suggested the use of such a shunt in patients with mitral stenosis and pulmonary venous hypertension. Gius (201) observed that the venous system depends for its compensation for loss of blood on: (a) the size and level of the vein occluded; (b) the number and capacity of the anastomoses and collaterals; (c) the ability of the vessels to dilate; (d) the degree of vasospasm; (e) the absence of pathologic changes such as thrombosis and inflammation in the distal veins both before and after ligation; (f) the demand placed on the distal circulation by physiologic activity; and (g) the effect of hydrostatic forces. Freeman (202) reported that Eck-fistula formation and simple portal vein obstruction have qualitatively the same effects on serum phosphatase and bengal rose dye clearance. Eck-fistula formation in adult dogs consistently reduced the bengal rose dye clearance and increased the serum phosphatase. The evidence indicates that neither liver function test is an index of hepatic failure.

In studying the changes in the volume of the forearm and hand following the release of an obstruction to the venous return, MacKay & Pickles (203) showed the occurrence of three phases: (a) a rapid primary decrement, followed occasionally by (b) an increase in volume, and finally (c) a secondary

decrement as the limb volume gradually returned to normal. Scott & Radakovich (204) demonstrated venous stasis in the lower extremities, even when the superficial veins can be neither seen nor felt. White & Warren (205) stated that the walking venous pressure test, which measures the fall in pressure in the superficial veins of the lower extremity during walking, is of great value in ruling out incompetency of the deep veins in situations in which more conventional tests are difficult to evaluate. In patients with pleural effusion, James (206) stated that the venous pressure always exceeded the pleural pressure. Volwiler and associates (207) found portal vein hypertension not to be an essential factor in the formation of ascites in the dog. Landis & Hortenstine (208) stated that more study is needed of the degree to which the moderator system of reflexes can ensure constancy of venous, as well as arterial, blood pressures. This is needed because of the fact that reduced cardiac competence, by increasing cardiac resistance to the flow of venous blood, may interfere with an otherwise sensitive mechanism.

Wilson (209) suggested three types of portal hypertension: (a) the intrahepatic type, (b) the extrahepatic type, and (c) the combined type. He presented a patient with cirrhosis of the liver with resultant portal hypertension on whom a splenorenal anastomosis had been made with good therapeutic result. Walker & Longland (210) found the venous pressure in the foot when standing still to be about 90 mm. of mercury in a man of ordinary height. During exercise (marking time) the venous pressure fell to less than 40 mm. of mercury. Glaser and associates (211) noted that the lungs and liver contain more blood when the skin is exposed to cool than to warm environments. Stürup & Højensgård (212) found that in patients with varicose veins, the pressure in the subcutaneous veins was not clearly influenced by the incompetent communicating veins in the standing position and during walking. They (213) also reported that in patients with varicosities, the pressure in the popliteal vein was equal to the calculated hydrostatic pressure in the standing position, and during walking the mean pressure remained unaltered. Davidson and associates (214) reported that cirrhosis impeded the circulation in the liver and elevated the pressure in the portal vein.

CEREBRAL CIRCULATION

Campbell and associates (215) noted that elevation of intracranial pressure in dogs was followed by bradycardia, lowered cardiac output, and increased mean pulmonary venous and arterial pressure during spontaneous as well as during artificial respiration. Gamble and associates (216) suggested that cerebral symptoms occurring at levels of headward centrifugal force in the range of 3 to 5 g may be due to changes of reflex origin. The electrocardiograms showed vagus block with marked bradycardia and periods of asystole, and indicated brain disturbance. Kety (217) reported that when hypertensives undergo a drop in arterial pressure as a result of differential spinal block, a fall in cerebral blood flow occurs and is associated with a feeling of faintness, nausea, or vomiting. By use of the nitrous oxide method for

measurement of cerebral flow in normal young men in the supine position, Scheinberg & Stead (218) noted that at rest 14 per cent of the cardiac output is devoted to the cerebral circulation.

Shenkin and associates (219) found that in normal subjects tilting the head up 20° does not change the cerebral blood flow; but tilting the head down 20° slightly reduces the cerebral blood flow. Wechsler and co-workers (220) observed that therapeutic doses of aminophylline produced marked constriction of the cerebral blood vessels and a real anoxia of cerebral tissue. In patients with cerebrovascular disease but with no alteration in their mental status, Scheinberg (221) found significantly lower cerebral blood flows, higher arteriovenous oxygen differences and higher cerebrovascular resistances than in normal young persons. Those with abnormal mental status resulting from vascular disease had significantly lower cerebral flow of blood, cerebral oxygen, and glucose utilizations, and higher cerebrovascular resistances than those with normal mental status or than young normal subjects. Their findings suggested that a decrease in cerebral blood flow might occur after stellate ganglion block. Kety (222) obtained 54 cc. per 100 gm. of brain per minute for human cerebral blood flow. This corresponds to 740 cc. per minute for a brain of average weight. Thompson & Rhode (223) found that pathologic unconsciousness does not occur following ligation of the anterior cerebral arteries in *Macaca mulatta*.

EFFECT OF CHEMICAL AGENTS

Marshall (224) reviewed the literature on dibenamine and found that dibenamine opposed chiefly the peripheral vasoconstriction which epinephrine induces. Banga and associates (225) obtained different physical properties for the collagen extracted from the Achilles tendon from that extracted from the aorta. The collagen of the aorta was neither viscous nor did it display double refraction of flow, while that of the tendon did. The molecules of collagen of the aorta are not threadlike but globular. Björkenheim & Hortling (226) observed that under the influence of tetraethylammonium, the leukocytes, including neutrophils and lymphocytes, decreased, reaching their minimum value 15 to 30 minutes after injection. The erythrocytes and reticulocytes were not regularly involved. Arnold & Rosenheim (227) found the action of pentamethonium iodide to be similar to that of tetraethylammonium chloride, but it is effective in smaller doses. Its effect lasts for at least one hour. Excessive fall in arterial pressure was its only observed serious toxic effect, which could be counteracted by epinephrine. Lewis & Ferguson (228) reported that intravenous injection of staphylokinase into the dog caused the appearance of active serum lysin accompanied by a fall in prolysin and antilysin. The blood became incoagulable, presumably because of lysis of the circulating fibrinogen. A precipitous fall of arterial pressure was observed. Redisch (229) believes that the usefulness of either male or female sex hormone as a drug in peripheral vascular disturbances has not been established.

MacKay & Pecka (230) suggested that, as measured by lung weight, a lesser degree of pulmonary edema is produced by toxic doses of *l*-norepinephrine than by smaller but toxic doses of *l*-epinephrine. A β -haloalkylamine adrenergic blocking agent prevents all the symptoms and the pulmonary edema produced by the toxic doses of either *l*-epinephrine or *l*-norepinephrine. Stutzman and associates (231) described a stable potent extract of *Veratrum viride* which, in dogs, produced hypotension, bradycardia and emesis. Sonnenschein (232) reported that intradermal injection of epinephrine caused local sweating. The response was not altered by atropine or tetraethylammonium chloride, but was diminished by procaine and inhibited by dibenamine. Bailey and associates (233) noted that temporary occlusion of the celiac and superior mesenteric arteries prevented alloxan diabetes in rabbits. Romney (234) described the spiral nature of the primary villus stem vessels and stated that the underlying mechanism suggests a trophic response to steroid hormones. Ambrose & DeEds (235) observed that rutin in doses of 100 mg. decreases the erythematous response to localized chloroform irritation as judged by the decreased diffusion of the intravenously administered trypan blue into the irritated areas. Karr & Hendricks (236) found that the toxicity of intravenously administered ammonium chloride depended on the rate of administration and was virtually independent of the total amount administered. However, the therapeutic value depends on the amount regardless of the rate. Swan (237) stated that the main effect of norepinephrine, when administered to normal people, was a peripheral vasoconstriction which led to a rise in both systolic and diastolic blood pressures. Bradycardia, probably of reflex origin, developed.

Rogers (238) noted definite improvement with increase in oscillometric readings in both legs of geriatric patients following the administration of priscoline, 25 mg. three to five times daily. Winter (239) noted that the antihistaminic drug, phenergan, in doses of 20 or 40 mg. per kg., failed to protect rats or guinea pigs against pulmonary edema induced by injection of ammonium chloride, and offered no protection against epinephrine-induced pulmonary edema in guinea pigs. Handley and associates (240) found that the glomerular filtration rate as measured by creatinine clearance was reduced by chronic dosage of mercurial diuretics administered to dogs intravenously.

By use of venous catheterization and a mercurial diuretic containing a radioactive isotope of mercury, Milnar and co-workers (241) measured the time course of the radiomercury and of the diuretic and compared their concentration in the renal or hepatic venous blood, in the arterial and venous blood of the extremities and in the urine. From these data the percentage extraction of mercury by kidneys, extremities, and liver was calculated. Friedell and associates (242) noted that intravenous administration of priscoline will alter the circulatory index as determined with radioactive phosphorus. Priscoline is more effective in conditions primarily due to interference with the blood supply than in severe conditions associated with causalgic

states. Chen & Russell (243) found diphenhydramine capable of converting the vasodepressor effect of epinephrine and arterenol in the dog under adrenergic blockade with SY-28 to a vasopressor effect. Barnett *et al.* (244) reported a rise in systolic, diastolic and mean arterial pressures, slowing of the heart, and reduction in blood flow to muscle and skin as a result of intravenous infusion of norepinephrine to healthy adults. Pugh & Wyndham (245) reported that spinal anesthesia caused a fall in blood pressure in hypertensive and normotensive subjects. Gersten and associates (246) produced significant increases in blood flow in the extremities which were treated with mecholyl ion transfer. The increase in blood flow was much greater when mecholyl ion transfer was given alone than when atropine sulfate was given intravenously five minutes before ion transfer. Wakim and associates (247), by intravenous administration of 50 mg. of priscol, produced a definite increase in blood flow in the forearms and legs, which lasted several hours.

ARTERIOVENOUS FISTULA

Lowenberg & Shumacker (248) reported in growing animals an increase in the circumference of the artery at the line of anastomosis comparable to the increase in the circumference of the unsutured portion of the artery. The artery anastomosed by end-to-end repair gains in strength, and a sutured artery withstands, without leaking, intraluminal pressure far in excess of systolic blood pressure. Van Loo & Heringman (249) suggested that the presence of an acute arteriovenous fistula causes (a) a reduction of the systolic, diastolic, and mean arterial pressures; (b) an increase in heart rate; (c) vasoconstriction in the periphery outside of the fistula circuit and a decrease in the returning venous blood from these regions; (d) unchanged central venous pressure and (e) increased cardiac output and stroke volume. Glenn and associates (250) demonstrated angiographically a narrowing of the aortic lumen at the suture line about one year after end-to-end anastomosis of the thoracic aorta in young dogs. Jordan (251) made arteriovenous shunts in hopelessly ischemic and/or gangrenous extremities. The legs grew warmer and gangrene spread was controlled. Wipf *et al.* (252) produced arteriovenous fistulas in large dogs by joining the common carotid artery and the jugular vein. A surprising result was the absence of hypertrophy and lack of increase in weight of the heart. This was attributed to the dogs' efficient compensation for the additional circulatory load.

Holman (253) emphasized that the important condition for the development of collateral circulation around an arteriovenous fistula is the ready access of blood to the site of the fistula by retrograde flow through a widely patent distal artery and its branches. The most effective deterrent to the development of collateral circulation is ligation of the artery just distal to the fistula, leaving no branches intervening between the fistula and the site of ligation. Shumacker & Stahl (254) noted cardiac enlargement in a large number of soldiers with peripheral arteriovenous fistula of short duration; the heart size diminished after surgical repair of the fistula. Bosher and

associates (255) reported that excision of femoral arteriovenous fistula caused a marked regression in the arterial collateral bed of experimental animals. Robertson and co-workers (256) presented a method for direct measurement of collateral blood flow in the presence of both experimental arteriovenous fistula and acute arterial occlusion. Their findings support the policy of delay in the treatment of arteriovenous fistula to allow maximal development of collateral circulation.

Callow & Welsh (257) demonstrated that arterial reunion by end-to-end suture, arterial hemograft bridge, and nonsuture vein graft was highly successful in clean wounds when performed immediately after arterial severance. Robertson and associates stated that among the factors concerned in the development of collateral circulation about a fistula, two are of primary importance: (a) the influence which the arteriovenous shunt exerts on the collateral bed by its regions of diminished peripheral resistance must have been present for a sufficient time to permit maximal dilatation and hypertrophy of these vessels; (b) for peripheral resistance to be diminished sufficiently, it is necessary that the fistula exceed a minimal size. Liebow *et al.* (258) noted that an extensive collateral circulation and large anastomoses develop between the bronchial and pulmonary arteries in chronic pulmonary disease and in certain forms of congenital heart disease. Huggins and associates (259), after experimentally increasing pulmonary vascular pressure in the dog, found the capacity of a pulmonary vein-azygos vein shunt to be up to 8 per cent of the total cardiac output. There was no consistent evidence that the presence of the shunt produced or added to the strain on the right ventricle or interfered with the filling pressure of the left ventricle.

SHOCK AND HEMORRHAGE

Oberg (260) made a study of the changes of erythrocytes, hemoglobin, reticulocytes, and platelets in rabbits after transfusions and repeated blood-letting for a period of one to one and one-half years. After repeated blood transfusions, there was a considerable decrease in the number of platelets. Stefanini & Petrillo (261) concluded that hypofibrinogenemia, a constant sign of hepatic dysfunction, was never per se responsible for hemorrhagic manifestations. The prothrombin level was low, and in all instances increased capillary fragility accompanied the hypoprothrombinemia. Possibly the deficient utilization of vitamin K by an impaired liver may be the underlying mechanism of the hemorrhagic manifestations of hepatic dysfunction.

In an excellent lecture on certain aspects of the nature and treatment of oligemic shock, Page (262) presents three possibilities to explain constriction of blood vessels when blood volume is reduced; namely, (a) physical factors, (b) active neurogenic contraction, (c) active humoral contraction.

Zweifach & Hershey (263) reported findings indicating that, irrespective of the initiating factor, the compensatory responses of the peripheral blood vessels can be altered in a predictable manner, according to the anesthetic agent used. Paine and associates (264) reported that pulmonary edema may

be induced in the heart-lung preparation (a) by lowering the plasma proteins through replacement of blood plasma with Locke's solution, or (b) by elevation of pulmonary vascular hydrostatic pressures following imposition of left ventricular overload. Hines & Parker (265) found that ascorbic acid was capable of changing quickly some defect in the capillary bed and was equally effective in patients with scurvy, diabetes, or vascular diseases, such as essential hypertension and arteriosclerosis.

Cohn & Parsons (266) described a method for maintaining the portal venous pressure at high levels and reported that under such circumstances acute experiment shock, which in control animals is irreversible, becomes reversible. Nelson and associates (267) noted that the infusion of hemolyzed blood in the dog produced a syndrome of prolongation of blood coagulation time, gastro-intestinal bleeding, and petechiae. Remington and associates (268) observed that prevention of vasoconstriction by use of dibenamine 15 mg. per kg. after hemorrhage severely reduced the lethal blood volume, but the animal would survive pressure and flow levels which would be fatal to the control. Hale (269) demonstrated that opaque medium injected into the brachial artery of a dog reached the coronary and carotid arteries almost immediately. Remington and associates (270) noted that vasoconstriction renders the animal more sensitive to reduction of blood volume so that the local fluid loss into the traumatized regions constitutes a lethal hemorrhage. They (271) reported that in early hemorrhage, cardiac output and resistance seemed reciprocally related. Ruiz Estrada (272) reported improvement in capillary fragility in patients treated with rutin or rutorbin. Frericks and associates (273) obtained no detectable change in capillary fragility, in capillary permeability, in retinal hemorrhages and exudate, or in petechiae in diabetic or in hypertensive subjects given 180 mg. rutin daily for one to three months when compared with similar patients given a placebo. Clatworthy & Varco (274) temporarily prevented mechanical shock in dogs by a small polythene shunt used to divert a portion of the blood around the cross-clamped thoracic aorta.

INFUSIONS

Martin and associates (275) described a method for constant intravenous infusion of bacteria and for bacterial counts at various sites in the circulation by venous catheterization. It provides a means of determining the site and quantitating the rate of removal of bacteria from the blood stream of intact animals. Deyrup & Walcott (276) found that when blood is mixed with strongly concentrated solutions of sodium chloride and the formed elements are subsequently resuspended in isotonic saline solution, a depressor substance is released from the cells. They (277) stated that the brief but profound hypotension which follows intravenous injection of hypertonic solutions may be altered as to timing and severity by admixture of the hypertonic agent with homologous blood prior to injection. Raisz and associates (278) examined vascular pressures and volumes after intravenous infusion of 1,100

to 1,600 cc. of a modified Locke's solution in dogs and obtained only a transient increase in the venous and arterial pressures and pulse rate.

THROMBOEMBOLIC DISEASE

Lumbar sympathectomy for far-advanced obliterative arteriosclerotic vascular disease revealed to Coller and associates (279), in a follow-up over a two and one-half year period, that 70 per cent of the group obtained some measure of alleviation of symptoms following operation. DeBakey & Ochsner (280) offer evidence that sudden complete blockage of the circulation by venous thrombosis is the primary factor in the mechanism involved in this ischemic disturbance. Tichy (281) concluded that a marked drop in the incidence of thrombosis of the leg veins can be expected be electrically stimulating the leg muscles during the time that circulation is impaired in patients undergoing operation. Hermann & Buchman (282) remarked that acute arterial occlusion is a real emergency and every method of promoting adequate circulation through the collateral arterial pathways should be instituted as soon as possible after the accident. Woodburne & Philpott (283) related nodular vasculitis to periarteritis nodosa or nodular nonsuppurative panniculitis. Kirk (284) suggested that early diagnosis and carefully planned long-term management can prevent many of the complications of diabetes. Anderson (285) concluded that arteriosclerosis in the diabetic should be studied only as one part of the much broader concept, vascular degeneration, and that cholesterol metabolism is probably but one factor in a quantitatively disordered lipid economy in which phospholipids play a large part.

A method for consistent production of atherosclerosis in the chick was standardized by Horlick & Katz (286) for (a) varying concentrations of cholesterol in the diet, and (b) time course of feeding. Moolten & Vroman (287) reported that marked platelet hyperadhesiveness predisposes to thrombosis. The severe pain resulting from acute arterial occlusion has been termed ischemic neuritis by Freeman and associates (288). They suggested that arterectomy is of value in the treatment of this type of pain through the interruption of some nervous reflex which originates from the thrombosed artery. To determine whether or not the degree of stasis present in varicose veins would increase fragility of erythrocytes, Mettier and associates (289) compared blood from varicose veins with cubital vein blood in 20 patients. They obtained no increase in fragility of erythrocytes in the varicose vein specimen. Pratt (290) concluded that sympathectomy should be used more widely and earlier in occlusive arterial disease. Its place in spastic syndromes has been established. Bierman (291) suggested that physical measures, such as the commonly used simple procedures and uncomplicated devices, are adequate both in the diagnosis and in the treatment of peripheral vascular disease.

The studies of McCormick & Holman (292) re-emphasize the importance of the kidneys in the pathogenesis of necrotizing arteritis and indicate that azotemia per se is not the "renal factor." Pedersen (293) found that in em-

bolism of the arteries of the forearm and of the leg below the knee, heparin-papaverine treatment is good and that the arteries are too small for operation. Wartman (294) described three cases of obstructive arteriosclerosis of the iliac and femoral arteries associated with extensive vascularization of the arterial wall. Novotny (295) demonstrated anatomically the presence of a gliding mechanism at the adductor canal between the femoral artery and this canal in normal persons. In persons suffering from thromboangiitis obliterans, this gliding mechanism is disturbed. McAllister & Waters (296) produced acute arterial and endocardial lesions by feeding toxic quantities of viosterol to thyroidectomized dogs. Fowler (297) made a survey of the literature on thromboembolism. Glaser (298) suggested that axillary thrombosis is a syndrome which should be considered in patients with pain, swelling, and tenderness in the axilla and arm. Boyd & Jepson (299) reported two cases of thrombosis of the external iliac artery and emphasized as diagnostic features the disappearance or marked diminution of pulses and oscillometric readings after exercise, followed by a rapid return to normal on resting.

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HEART

BY HOWARD B. BURCHELL

Division of Medicine, Mayo Clinic, Rochester, Minnesota

HEART RATE, CARDIAC INNERVATION

Smithwick and co-workers (1) have extensively investigated the human heart rate, particularly as affected by sympathectomy. Evidence is presented that the cardioaccelerator fibers in man arise from the second to the fifth thoracic segments of the cord inclusive. The persistent resting tachycardia characterizing a certain group of subjects was found to be due to a combination of increased sympathetic and decreased vagus tone. Malmö & Shagass (2) have studied the heart rate in relationship to age, sex, and stress, the last being an imposed painful stimulus. The variability of the heart rate under the influence of painful stimuli seemed to decrease linearly with age, a finding which might be explained in terms of diminished influence of the autonomic nervous system with increasing age. In a patient with incomplete heart block and interference dissociation, Matsuda & Tomono (3) found a possible inhibitory effect of ventricular systole upon the rate of impulse formation in the sinus node. Atropinization abolished the effect. The effect of warming and cooling the region of the sinoatrial node with an intracardiac thermode in the intact animal has been reinvestigated by Hellerstein & Liebow (4). Acceleration and slowing were related to warming and cooling respectively, and displacement of the pacemaker to a different site on cooling the region of the sinoatrial node was observed.

Aviado and co-workers (5), by perfusing individual segments of the heart and lungs of dogs, localized the receptors for various vagus-dependent reflexes. Pressure increases in the right atrium caused a reflex bradycardia, an effect opposite to the classical "Bainbridge reflex." A drop in systemic blood pressure occurred independent of the bradycardia. Pressure increases in the pulmonary artery also caused a reflex slowing of the heart rate. Pardo and co-workers (6) have noted that there were certain sympathetic pathways to the heart which were not blocked by tetraethylammonium salts. While salts of this drug prevented acceleration of the sinoatrial node resulting from pre-ganglionic sympathetic stimulation, they failed to block inotropic and chronotropic effects on the atrioventricular node and ventricles. Further, cardiac acceleration caused by cephalic asphyxia also was not abolished by the injection of tetraethylammonium salts but could be abolished by crushing the sympathetic preganglionic rami. Middleton and co-workers (7) have observed a positive inotropic and chronotropic effect on both atria and ventricles on excitation of the cervical portion of the vagus in the completely atropinized isolated cat heart. An epinephrine-like substance was found to be released in the heart and the results were interpreted as indicative of the existence in the heart of adrenergic ganglia con-

nected with the vagus. Lockett (8), in a carefully controlled study of the responses of the heart rate and systolic blood pressure to a series of sympathomimetic amines in the anesthetized atropinized dog, noted that following sympathectomy the increase in heart rate after administration of epinephrine was augmented. After sympathectomy, norepinephrine was more active in increasing the systolic blood pressure than was epinephrine.

The effect of hypoxemia on the supraventricular pacemakers, particularly in regard to an increased sensitivity to acetylcholine, has been studied by Callebaut and co-workers (9). The sensitivity to acetylcholine was related to a probable direct inhibition of cholinesterase by the hypoxia. Raab & Lepeschkin (10) have reported that the cardiac acceleration produced by epinephrine or by stimulation of the cardiac sympathetics could be diminished or abolished by nitroglycerine. It is inferred that nitroglycerine might thus prevent or relieve anginal pain by abolishing the effect of sympathomimetic amines originating in the heart muscle. Knox (11), studying the increase in ventricular rate with exercise in individuals with atrial fibrillation, found maximal heart rates that were higher than in normal individuals. Neil & Zotterman (12) studied the cardiac vagal afferent fibers in the cat and dog and obtained further evidence that the large afferent fibers of the cardiac vagus originate in the atria and that they act as stretch receptors. Small fibers originating in the ventricle were shown to be related to a cardiac depressor reflex.

Paes (13) has reported that extracts of nodal tissue from the sheep's heart caused the asynchronous contractions of the isolated rabbit atrial myocardium to be changed into synchronous rhythmic activity.

ARRHYTHMIAS

Of great interest and popularity during the past year have been the reports of Prinzmetal and co-workers (14) and of Scherf & Terranova (15) on experimental atrial flutter and fibrillation. From the work reported, it appears that experimentally produced atrial flutter of specific types is related to an ectopic focus. Prinzmetal's conclusions are based upon detailed observations on the mechanical activity of the atria as shown by high-speed photography and by studies of electrograms. The thesis of a unitary nature of the atrial arrhythmias is stated rather dogmatically, in brief, that the difference between extrasystoles, atrial tachycardia, flutter, and fibrillation is only one of rate of discharge of the ectopic focus. In man with atrial flutter, records taken from the precordium and esophagus are said to indicate origin of the impulse from a single focus. The work of Scherf & Terranova (15) on aconitine flutter, in which the effects of cooling the atrium and of vagus stimulation are well shown, contains excellent experimental data supporting their belief that in this form of flutter there is no large circus pathway. They suggest that in atrial flutter there is a constant stimulus, and the response of the atrium to the stimulus depends only on the length of the refractory phase of its muscle. Scherf, with other workers (16), has reported that in atrial fibril-

lation caused by electrical stimulation or acetylcholine, more than one center of rapid stimulation is active, as cooling the site of stimulation or the site of the application of the drug did not stop the fibrillation. Van Dongen & Taal (17) have reviewed their work concerning the action of antifibrillatory drugs, and, as a complete parallelism existed between the neutralization of fibrillation and suppression of heterotopic rhythms, they concluded that the mechanism of fibrillation had to be explained by the existence of multiple heterotopic centers. The reviewer believes that the evidence is not yet available on which to discard entirely the theory of a circus rhythm in all forms of atrial flutter as is found, for instance, in the experimental type so well described and documented by Rosenblueth & Ramos (18). In addition, Grishman and co-workers (19), studying atrial vectorcardiograms obtained from a man with flutter, came to the conclusion that a circus movement was present.

Horlick & Surtshin (20) noted, in dogs, that administration of acetylcholine was more likely to cause atrial fibrillation when the animal was anemic. The sensitivity to acetylcholine paralleled the severity of the experimental anemia and was attributed to a myocardial anoxia. Another case of atrial fibrillation following immersion hypothermia has been reported by Graybiel & Dawe (21). Grant and co-workers (22) attempted unsuccessfully to elucidate the nature of the atrial fibrillation occurring in hypothermia by studying the sensitivity of hypothermic dogs to vagal stimulation following the injection of epinephrine.

Hoff & Stansfield (23) have reported studies on ventricular fibrillation induced by cold. Local cooling of the dog's ventricle to 10°C. or below facilitated the development of ventricular fibrillation in response to a single threshold induction shock stimulus of the noncooled region during early diastole.

CARDIAC DYNAMICS

Concerning the measurement of intracardiac and intravascular pressure, Ellis and co-workers (24) have described an instrument with a tiny manometer placed at the end of a sound or catheter, with which high-fidelity artefact-free tracings have been obtained. Hansen (25) has discussed in detail the measurement of pressures in the human organism. Buchbinder & Katz (26) published curves of intraventricular pressures of the right and left ventricles obtained by direct transthoracic puncture in man. Many extrasystoles were present. The pressure developed by each postextrasystolic beat was found to be related to the duration of the immediately preceding diastole.

Investigations of the effect of inspiration on right atrial inflow have been reported by Opdyke & Van Noate (27); they expressed the belief that effective right atrial pressure increases during inspiration. While such an effect might be related to increased pulmonary resistance or increased atrial inflow, the latter was believed to be most likely. Bauereisen and co-workers (28) have carried out further studies on the nature of the marked variations in

arterial pressure related to slow breathing with a partially obstructed airway.

Bakos (29) has found that, despite complete inactivation of the right ventricle by severe cautery, no change occurred in peripheral venous or pulmonary artery pressures. Rodbard & Wagner (30) were able to shunt the venous blood from the right atrium to the lungs through the pulmonary artery. Animals were living up to two months thereafter with the right ventricle bypassed and functionless. Sawyer (31) reported that, in patients with chronic constructive pericarditis, the right ventricle was accomplishing very little work.

Prec and co-workers (32) have given the values for the heart's kinetic energy, expressed as per cent of the total energy, as 2.4 to 12.5 per cent for the right side of the heart and 0.25 to 2 per cent for the left side. The size of the aorta and pulmonary artery was determined by angiocardiography and the blood flow by the Fick principle utilizing cardiac catheterization data. Gauer (33), studying the intraventricular and aortic pressures of animals in shock, noted a phenomenon in which the aortic pressure might reach only a peak of 50 mm. following which the ventricular pressure would progress to 120 to 200 mm. of mercury. The explanation offered was that the ventricle continued to contract isometrically after expelling its pathologically small amount of blood.

Bruce and co-workers (34) have reported the results of investigations on the normal respiratory and circulatory pathways of adaptation in exercise. A statistical analysis of a large series of observations showed a 7 per cent increase in cardiac output for every 10 per cent increment in oxygen consumption. Graybiel and co-workers (35), studying partial acclimatization of 4 healthy young men to simulated high altitudes over a period of a month at 22,500 feet found that the heart shadow decreased slightly in size. Wilson and co-workers (36) rapidly injected large amounts of plasma in convalescents; while the sudden increase in blood volume was accompanied by temporary increases in pulse rate, blood pressure, and venous pressure, the procedure was well tolerated.

A carefully controlled study of the work performance of six subjects before, during, and after three to four weeks in bed has been reported by Taylor and co-workers (37). The most dramatic change caused by rest in bed was the increase in work pulse rate. A significant decrease in heart size occurred. Kjellberg and associates (38) have reported a good correlation between the total amount of hemoglobin and the pulse rate at rest or exercise, and also that the amount of hemoglobin and blood volume correlated well with the heart volume determined roentgenologically. These investigators (39) have also found evidence of a great increase in systolic emptying of the left ventricle during work, as evidenced by electrokymograms. There was an absence of a direct correlation between the heart volume and the stroke volume, which might have been expected if the stroke volume were regulated in a simple relationship to Starling's law of the heart. The possi-

bility of a vegetative regulation of the heart which affects its volume contraction and is mediated through the nervous system is suggested.

Pertinent to Kjellberg's hypothesis are the observations of Peterson (40) in which evidence is presented that increased vagal activity caused a primary weakening of the ventricular contraction. This phenomenon seemed to have been present in man following stimulation of the carotid sinus and following stimulation of the mesenteric receptors. The effects were contrasted to the strong ventricular beat following prolonged diastole related to premature or missed contractions. Of interest in this problem are the observations on the role of vagal activity in experimental pulmonary embolism—reported by Cort & Davis (41). Their experiments indicated that increased vagal activity plays an important role in the rapid decline in systolic blood pressure and in the electrocardiographic changes. The survival time of vagotomized animals was significantly longer.

Friedman (42) has found good correlation between the fluid displacement of the removed heart and the roentgenologic determination of heart volume at postmortem examination. More than 50 per cent of the total volume of the heart during life was believed to consist of residual blood. Van Loo & Heringman (43) have studied the circulatory changes in the dog produced by acute arteriovenous fistula. In spite of the great increase in blood flow, the "central venous pressure" did not change. Left atrial pressure was not measured. Gorlin & Haynes (44) have obtained reasonable values of the cross-sectional area of the human mitral valve, using the basic data on flow and pressure gradient obtained by cardiac catheterization.

Storstein (45) reinvestigated circulation times to determine whether they were largely dependent upon the size of the heart, and failed to confirm this relationship. Differences in electrical conductivity of the body during the cardiac cycle ("rheocardiograms") have been obtained by Polzer & Schuhfried (46). Characteristic changes are claimed to occur with disturbances of cardiac dynamics.

CORONARY CIRCULATION

The functional significance of experimentally produced intercoronary anastomoses in the pig has been investigated by Blumgart and co-workers (47). It was found that twelve or more days of 75 per cent narrowing of a vessel were required to produce a sufficiently rich anastomotic network to protect the myocardium from damage and to permit survival after superimposed acute complete occlusion. Vineberg (48) and Glenn and co-workers (49) have reported experiments in which anastomoses were seen to develop between an internal mammary artery transplanted into the myocardium and the coronary vessels. While the exact mechanism underlying the protection of the heart previously subjected to procedures causing increases in coronary sinus pressure is obscure and unlikely to be related to retrograde flow, there have been further excellent studies on the problem. In particular, McAllister and co-workers (50) have carried out meticulous work on the "revasculariza-

tion" of the heart by a free vein graft from the aorta to the coronary sinus.

Employing the method of angioplethysmography, Smith (51) has evaluated the responses of isolated coronary arteries to various drugs. Epinephrine did not produce a uniform response. Acetylcholine produced consistent coronary vasoconstriction, as did histamine. A rotameter was used to study coronary inflow by Winbury and co-workers (52), who reported that the flow was increased by epinephrine, acetylcholine, and histamine, while it was decreased by pitressin.

The most interesting papers of the year dealing with coronary blood flow are those concerned with the utilization of nitrous oxide to determine the coronary flow. The work was extended to unanesthetized dogs by Spencer and co-workers (53), who found that the variation in flow was greater than the reported values for animals under anesthesia. The calculated left ventricular efficiency ranged from 20 to 38 per cent. Individual determinations of the blood flow per 100 gm. of left ventricle varied between 80 and 220 cc. per minute. The application of the technique to man has been reported by Bing and co-workers (54) who found that the mean values for blood flow and oxygen consumption per 100 gm. of ventricular muscle were equivalent to those for the dog, though slightly lower. There are many findings in this study that are provocative of thought as, for instance, the differences found between essential hypertension and coarctation of the aorta. In the former, the flow and oxygen consumption per unit of ventricular muscle were normal, while in the latter these values were markedly elevated. It was postulated that when the increase in cardiac load is prolonged over months or years, the heart meets its increased energy requirements not by a rise in oxygen consumption per unit weight, but by an increase in the total myocardial mass. In congestive heart failure, despite clinical and radiologic evidence of left ventricular hypertrophy, the left ventricular oxygen consumption per 100 gm. of muscle was only slightly increased. It was concluded that Starling's law might not be applicable to an anatomic enlargement, as it is to dynamic dilatation or stretch. In any critical analysis of results obtained with this procedure, reference to the basic principle on which the nitrous oxide technique is based is necessary [Eckenhoff and co-workers (55)]. As rarities, it might be mentioned that peculiar results in man could be related to persistence of a left superior vena cava that drains into the coronary sinus or to a free communication between the left atrium and coronary sinus. Green and co-workers (56) found sizeable differences between the volumes of coronary blood flow simultaneously determined by the nitrous oxide method and a rotameter. Wégria and co-workers (57) reported that in experimental atrial fibrillation there is marked drop in arterial pressure and in coronary blood flow with, however, both factors returning toward their control levels within a few seconds. The change is probably related more to ventricular rate than to atrial fibrillation per se. Bulbring and associates (58) have expressed the belief that nicotine may cause coronary vasoconstriction through stimulation of the secretion of a principle by the posterior pituitary. The degree

of reduction in coronary flow necessary to produce electrocardiographic changes has been investigated by Wégria and co-workers (59), the measurements having been made with a rotameter. A clinically oriented review of the physiology of the coronary circulation has been published by Eckenhooff (60).

CARDIAC OUTPUT

Seely & Gregg (61) have been able to measure the cardiac output directly by the introduction of a rotameter in the pulmonary artery circuit. A good correlation has been found between the cardiac output as determined by the Fick procedure and by the direct rotameter method (62). Determinations of cardiac output from pressure pulse contours by the method of Hamilton and Remington has been reinvestigated and found valid by Remington and co-workers (63) and Huggins and co-workers (64). Measurements of input flow, made by a rotameter in the hands of Huggins and co-workers (65), agreed with the simultaneously determined cardiac outputs by the direct Fick method. Martin and co-workers (66) have reexamined the problem of obtaining values for the carbon dioxide content of venous blood by equilibration of alveolar air and its application to determinations of cardiac output, and successful experiments have been reported. Elam and co-workers (67) have modified and applied the oximetric method of Matthes in the determination of oxygen saturation of mixed venous blood and in turn to calculations of cardiac output. The method was used successfully under conditions of mild exercise. Knutson and co-workers (68) found good plateau levels for the venous oxygen level, as determined oximetrically using Elam's procedure, in half of the subjects studied. According to Sutton and co-workers (69), detectable complete circulation occurred as early as the seventh to the ninth second. The method used was a steady injection of tagged erythrocytes into the main pulmonary artery, during which time serial samples of right ventricular blood were taken. Nylin & Celander (70) have treated mathematically the dilution curve of the specific activity of the erythrocytes in the arterial blood after intravenous injection of erythrocytes labelled with P^{32} . By such analysis, the residual blood in the heart and lungs ("thoracic pool") was found to amount to 30 per cent of the total circulating blood volume. Mathematical analysis of dilution curves as used for the calculation of cardiac output have also been carried out by Cyvin (71). Rashkind & Morton (72) compared the constant and instantaneous injection techniques for determining cardiac output by the dye dilution method and it was believed that the constant intracardiac injection technique gives results as valid as does the instantaneous injection method. Werkö and co-workers (73) have reported an excellent correlation between values for cardiac output determined by the direct Fick and by the dye injection principle. Dye injected into the pulmonary artery gave arterial dilution curves almost approaching zero before recirculation began.

The cardiac output in normal pregnancy has been investigated by Palmer

& Walker (74) and by Hamilton (75) utilizing the cardiac catheterization technique. The output was moderately increased early in pregnancy with the maximal circulation rate occurring at about the sixth month. May and co-workers (76) found that high spinal anesthesia in normal and hypertensive patients often caused significant changes in arterial pressure without any significant fall in the cardiac output. Asmussen & Vinther-Paulson (77), in studying the circulatory adaptations to arterial hypoxemia as produced by carbon monoxide poisoning, found only slight increases in the cardiac output as part of the compensatory mechanism. It was mentioned that the nature of the stimulus for increased cardiac output remains very obscure.

Ballistocardiograms.—Starr and co-workers (78) have carried out mathematical analyses of the forces that produce the ballistocardiogram. In a dramatic exposition paralleled by the dramatic method of imparting energy to the syringes giving the stroke volumes into the great vessels of corpses, it was found that the recorded ballistocardiograms, excluding an I wave, were similar to constructed curves based on the derived rates of change in acceleration. Different types of ballistocardiographs and analysis of the curves obtained on them are reported by Krahel (79) and by Ernsthausen and co-workers (80). Paine & Shock (81) have found an excellent reproducibility in estimations of cardiac output made with the ballistocardiograph. A standard meal caused an average 12 per cent increase in cardiac output. Less variability in the cardiac output was encountered with the use of the ballistocardiograph than with the venous catheterization technique. Ballistocardiographic tracings characteristic of coarctation of the aorta have been discussed by Murphy (82) and by Nickerson and co-workers (83). The normal K wave was absent, but appeared after surgical correction of the aortic stricture. Brown and co-workers (84) have reported abnormal ballistocardiographic records in patients with angina pectoris, particularly during the expiratory phase of respiration. Their work supports previous investigations claiming that an abnormal ballistocardiogram may indicate predisposition to progressive coronary disease. Berman and co-workers (85) reported that patients with angina were unable to increase their cardiac output significantly following meals in contrast to the response of normal subjects. Stevenson and co-workers (86) have studied the circulatory dynamics before and after exercise in subjects with and without structural heart disease during anxiety reactions. By ballistocardiographic methods, it was determined that the cardiac load was more likely to be greatly increased from anxiety than through the ordinary physical exertions of everyday life.

Electrokymography.—The general principles and application of electrokymography have been discussed by Boone and co-workers (87). It was reaffirmed that the ventricular isometric relaxation phase may be longer in diseased hearts. Lewis & Terry (88) have appraised the present clinical status of the method. They expressed the belief that, as a rule, bundle branch block was accompanied by significant differences between the rising phases of the pulmonary and carotid artery pulses. Andersson (89) described a de-

sign for an electrokymograph and published a special study (90) of the records of atrial movements. In 45 of 50 cases electrokymographic atrial contours in the region of the left atrial appendage were obtained. Fabricius (91) has found the duration of the presphygmic period to average 0.06 second with a range of 0.02 to 0.08 second. Soule and co-workers (92) have applied the method to the study of mitral valve disease and frequently have found evidence of regurgitation. Schwedel and co-workers (93) studied patients having bundle branch block and could establish no correlation between electrical and mechanical phases of the cardiac cycle. Nor was a characteristic electrokymographic pattern seen in the Wolff-Parkinson-White syndrome, the latter observation being in accord with that of Dack and co-workers (94). Heyer and co-workers (95), studying patients with aortic insufficiency, noted in the aortic tracings absence of the incisural markings, a rapid decline in volume in early diastole and a prolongation of ejection.

Electrokymographic studies of the cyclic density changes in the lung have been carried out by a number of investigators. Kjellberg and co-workers (96) believed it possible to demonstrate a relationship between the pulmonary blood content and the volume and rate of filling of the left ventricle. Jorgens and co-workers (97) discussed the "densigrams" obtained from the peripheral portion of the lung in different cardiac conditions. Gillick & Schneider (98) have attempted determinations of pulmonary arterial pressure based on the abolition of pulsations in the pulmonary field when patients exhaled against a resistance, and reported inconstant results. A parallel study of the relationship between increases of expiratory pressure and a pulmonary expansile pulsation utilizing, however, the roentgenkymogram, has been made by Thurnher & Weissel (99). Using the electrokymograph to determine the variations in central density of the heart, Ring and co-workers (100, 101) have been able to determine the stroke volume of the dog's heart as accurately as by the direct Fick or the dye dilution method. Dack and co-workers (102) have reported the superiority of the electrokymograph over the roentgenkymograph in demonstrating paradoxical movement related to myocardial infarction.

ELECTROCARDIOGRAPHY

Curtis (103) has found it possible to study the electric potentials of a small number of fibers of the turtle heart. He was mainly interested in determining whether a long-continued depolarization was a true cellular phenomenon of heart muscle, and his experiments seemed to establish the fact. Occasionally, injury potentials as high as 10 mv. were obtained, but it was emphasized that, since there was so much fluid shunting the muscle fibers, even the maximal potentials obtained represented probably only a small fraction of the true resting and action potentials of the membrane. Rothsuh (104, 105) has found maximal injury potentials of 50 to 60 mv. in the frog heart. The magnitude of the injury potential and its rate of disappearance were dependent upon the nature of the injury. Woodbury and co-

workers (106) were able to introduce microelectrodes into the interior of frog myocardial fibers. The mean resting potential was 62 mv. A reversal of the membrane polarity was recorded during activity, the mean value of the action potential being 80.8 mv. An interesting transient hyperpolarization was recorded in recovery. Curtis & Travis (107) were able to dissect out strands of the false tendons of the ox heart and study their electrical characteristics. It was concluded that the Purkinje system of the ox heart was physiologically qualitatively identical to cardiac muscle. Schaefer & Trautwein (108), by employing microelectrodes a fraction of a millimeter apart, have recorded the potentials over the surface of the dog heart during excitation. The charted results indicate that the spread of excitation occurs along the length of myocardial fibers. The velocity of the excitation wave averaged 0.88 m. per sec. Sodi-Pallares and co-workers (109) have determined the point on a unipolar electrogram which represents the arrival of the excitation at the subepicardial muscle. By ingenious transfer of time points from bipolar direct electrocardiograms to lead II and then to the unipolar curve, it was found that the lowest part of the intrinsic deflection, or the lower third of the unipolar curve, corresponded with arrival of excitation at the subepicardial muscle. Sodi-Pallares and co-workers (110) have reinvestigated the times of arrival of the excitation wave over the ventricular epicardium of the dog using direct unipolar leads. The last parts of the heart to be activated were the pulmonary conus and portions of the lateral and diaphragmatic surfaces of the left ventricle. Direct electrograms taken from the surface of the heart by Hein & Reavis (111) in one patient during surgical treatment were similar to the precordial V leads of corresponding position. Pruitt and co-workers (112), having noted that extensive injury to the endocardium of the left ventricle of dogs produced no greater widening of the QRS complex than was present in bundle branch block, studied the propagation of the excitatory process in strips of ventricular muscle. No evidence of endocardial, specialized, rapidly conducting tissue was discovered.

Akman and co-workers (113) have reported that heating the epicardial surface caused the T waves to be more positive, whereas cooling caused them to become more negative. The experiments gave support to the concept of the existence of an endocardial-epicardial gradient during the repolarization process. Further observations in the potential variations within the cavities of the right side of the human heart have been reported during the past year by Kert & Hoobler (114) and by Schlesinger and co-workers (115). Intracavity electrocardiograms of the left ventricle as well as those from the right ventricle have been reported on by Zimmerman & Hellerstein (116). The left cavity potential was usually a Q-S deflection, though in one case curves from the apex showed a definite R followed by a deep S. Premature beats produced a wide Q-S pattern within the cavity. Kossmann and co-workers (117) observed a transient wide Q-S deflection with a short P-R interval while studying the electrocardiograms of the cavity of the right ventricle and were alert to exploit its possibilities in an explanation of the

Wolff-Parkinson-White syndrome. The favored explanation offered was that the catheter increased the irritability of a ventricular center which then was discharged prematurely by a mechanical or electrical effect of atrial systole. The possibility of a supernormal conduction on the right side was not discussed.

Wilson & Bayley (118) have presented a mathematical treatise concerning the electrical field of a dipole moved from a centric to an eccentric position in a spherical medium. Grant (119), assuming that the mean cardiac potential at any time could be represented by a dipole and that the volume conductor was homogeneous, studied the pattern of the projection of lines representing zero isopotentiality of such a dipole on the surface of a cylinder. The line of zero isopotentiality on the surface of the cylinder or later when it was transferred to a chest was called the "null contour." The distribution of the "null contours" obtained from the calculated mean spatial QRS and T vectors was found to coincide with the pathways of transitional QRS and T complexes as determined by unipolar leads from all surfaces of the chest.

Oppenheimer and co-workers (120) have investigated the influence of introducing carbon dioxide into the right ventricle upon the electrocardiogram. By this means there was effected an insulation of the endocardial surface of the free wall of the right ventricle, and the representation of potentials from the right wall in the peripheral electric field was markedly distorted or annulled. Mauro and co-workers (121) have found marked asymmetric distribution over the thorax of equipotential lines in bundle branch block, which was offered as evidence that at no time in the cardiac cycle does a surface doublet distribution exist. Bryant and co-workers (122) have reinvestigated the results of varying the resistances leading to a central terminal (Wilson). When the resistances were eliminated, the potential of the central terminal was determined by the relative magnitudes of the resistances of the skin underlying the electrodes, and there seemed to be a slight practical difference in the clinical records in 1 out of 10 subjects. Jeanneret (123) has also carried out investigations on the influence of varying the resistances to the central terminal.

Further work on spatial vectorcardiography has been carried out by a number of teams of investigators. Conway and co-workers (124), using a previously described electrode relationship in which the fourth electrode is placed on the back to give a tetrahedron arrangement, give data on the normal spatial relationship of the P, QRS, and T potentials. Pantridge, working with others (125) in the same laboratory, has studied the spatial electrocardiogram of left bundle branch block. Their illustrations of the conventional electrocardiograms indicate that the diagnosis of left bundle branch block has not been narrowly restricted to exclude patterns of left ventricular hypertrophy and previous myocardial infarction with increased widths of the QRS complex. Jouve and co-workers (126) have studied the atrial vectorcardiograph and assigned to the afferent and efferent branch a suggested location of the excitatory potential. Genecin and co-workers (127) have indicated pro-

gression of their work determining the best type of peripheral electrode placement. Kossmann (128) has mentioned that he has registered the potentials related to P wave, QRS, and T wave separately. Levine & Schmitt (129) have presented the electrocardiogram in stereoscopically correct pattern in space. The problem of the correct interpretation of incomplete right bundle block has been discussed by Barker & Valencia (130) and they have noted that this may occur without any evidence of heart disease.

Simonson and co-workers (131) have made a careful study of the intra-individual variability of the electrocardiogram and arranged the various items measured in relationship to their consistency. One finding of importance was the indication that the K value as obtained as an index of electrical systole was of low consistency.

Johnson and co-workers (132) have found only rough correlation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary artery pressure in patients with chronic pulmonary disease. The electrocardiogram thus could not be used to rule out significant hypertension in the pulmonary circulation. However, when the pattern of right ventricular hypertrophy was present, it indicated a severe degree of pulmonary hypertension. Goldman and co-workers (133) reported on the electrocardiographic abnormalities seen in 50 patients during cardiac catheterizations. Ectopic beats were seen in the majority of the patients. Partial atrioventricular block and transient right bundle branch block were seen in a few.

Measurements of the Q-T interval continue to engage the interest of many investigators. Frequently the Q-T interval has been measured to a degree of refinement difficult of achievement even with Bazett's original projection technique. The term "corrected Q-T interval" meaning the K value of Bazett's formula has crept into the literature and it is felt that such practice should be abandoned; K values should be reported as indices. In an understanding of normal Q-T intervals, the paper of Alimurung and co-workers (134) may be instructive, the mean of the K values in normal children being 0.404 with a standard deviation of 0.026. About 95 per cent of the normal values were within boundaries of K plus or minus twice the standard deviation, that is, between 0.352 and 0.466. DeLalla & Brown (135) have reported observations on the effect of respiration on the Q-T interval. Yu and co-workers (136) have studied the Q-T interval in normal subjects and in various types of cardiac disease during exercise. A markedly increased Q-T:T-Q seemed to be related to the development of anginal pain. An inverse relation existed between the duration of exercise tolerated and the incidence of abnormal systolic indices. Benjamin (137) found the duration of the Q-T interval to be normal in pregnant women. Pokress & Goldberger (138) found that during active rheumatic fever prolongation of the Q-T interval was not invariable but frequently occurred, a finding consistent with that of Craige and co-workers (139). Krasonoff (140) found the Q-T interval to be abnormally long in patients with myocardial infarction. The differentiation of prolongation of the Q-T interval in hypocalcemia from that in hypokotassemia has

been carefully described by Ernstene & Proudfit (141). The hypocalcemic electrocardiogram has also been studied by Ljung (142), and the hypopotassemic electrocardiogram has been discussed by Bellet and co-workers (143). Lithium was found by McKusick (144) to have an effect on the electrocardiogram similar to that had by hyperpotassemia.

Of both physiologic and clinical interest are the recent reports indicating that patients with normal hearts may show electrocardiographic changes suggestive of coronary insufficiency under conditions of either exercise as reported by Master and co-workers (145) or emotion as reported by Wolff (146). Pordy and co-workers (147) have reported that dihydro-ergocornine will prevent such abnormal electrocardiographic changes following exercise in patients with functional heart disturbances. Ergotamine tartrate was used for making a distinction but had to be abandoned because of its angina-producing properties. Russek and co-workers (148) found that papaverine and nitroglycerine were of some effect in the prevention of the abnormal electrocardiographic response to standard exercise in patients with coronary disease. Whiskey failed to produce significant benefit. Dewar & Grimson (149) found that both nitroglycerine and khellin were much less effective in preventing electrocardiographic changes produced by exercise in patients with coronary disease than they were in preventing the pain response.

Penneys (150) has analyzed the response to induced anoxemia and the effect of adding a constant percentage of carbon dioxide to the inspired gas. Addition of carbon dioxide prevented many symptoms but had little effect on the alteration of the RST segment produced by the anoxemia. With Thomas (151), Penneys reported that the degree of cardiovascular response was closely related to the level of the arterial saturation. Mathers & Levy (152) found no optimal range of the oxygen saturation which might be used as the stress level for the production of diagnostic electrocardiographic changes in patients with coronary disease. Of interest in connection with the orientation of the boundary zone of injury in induced myocardial ischemia is the report by Wener and co-workers (153) in which an elevation of the RST segment in esophageal leads was consistently associated with segment depressions in the standard and precordial leads. In fatal cases of massive pulmonary embolism Dack and co-workers (154) observed the frequent occurrence of the electrocardiographic pattern of myocardial ischemia. The main predisposing cause was believed to be the hypotension of the shock state. In respect to electrocardiographic effects of anoxia, Åkerrén (155) has reported the marked changes which occur in prolonged asphyxia neonatorum. The effect of experimental hypothermia on the electrocardiogram has been studied by Lange and co-workers (156). It was believed that the changes in rate and conduction were directly the result of cold; prolongation of the Q-T interval, partly the result of anoxia; and the T wave changes entirely the result of anoxia. The effect on the electrocardiogram produced by preparations of ergot was reported by Rothlin & Cerletti (157). Suter and co-workers (158) have described the effects of the cardiac glycosides on the

electrocardiogram in therapeutic, toxic, and lethal phases. Morphologic changes of the heart muscle caused by the larger doses over a period of time are described. In a patient having shown the electrocardiographic changes of hypopotassemia, Perkins and co-workers (159) have reported focal myocardial necrosis. Studies of the normal electrocardiogram in infants and young children have been reported by Tudbury and co-workers (160), Maroney & Rantz (161), and Switzer & Besoain (162).

PHONOCARDIOGRAPHY

The necessity of good apparatus and extremely careful technique in the recording of the heart sounds and murmurs is discussed by Leatham (163). The use of various filters is described and excellent illustrations are given. Cowen & Parnum (164) have claimed that no clear-cut distinction between the systolic murmurs found in valvular and congenital heart disease and the innocent murmurs of normal hearts could be established by the timing of the murmurs alone. Ernsthausen (165), in a physical treatise dealing with the cardiac activity as an oscillating sequence, discusses the difficulties of determining the origins of the vibrations within the thorax. Records were made of chest wall movement, pressure changes within the esophagus, and volumetric changes of the thorax; wave forms roughly similar to the heart sound were found. In a clinically valuable report, Alimurung and co-workers (166) have reported on variations in the first apical sound simulating the so-called pre-systolic murmur of mitral stenosis. Eight cases are described in which a pre-systolic murmur was considered present by clinical auscultation but not confirmed by phonocardiographic technique. Esophageal phonocardiography has been attempted by Miller & Groedel (167), and in spite of technical difficulties, adequate records were sometimes obtained. Of the greatest physiologic interest was the recording of vibrations believed to indicate the closing snap of the atrioventricular valves, the opening snap of each semilunar valve and the constant recording of an atrial sound. Zinsser & Kay (168) have utilized the Valsalva procedure as an aid in the anatomic localization of cardiovascular murmurs and sounds. Following a period of straining, murmurs derived from the pulmonary circulation returned immediately, while those derived from the left side of the heart returned only after an appreciable delay. Rytand (169), using the criteria of the amplitude of the recorded vibrations in phonocardiograms, found that in atrial fibrillation, short diastolic periods were followed by a louder first sound than when the cycle was long. The findings were cited as further evidence that the first sound is louder when onset of ventricular systole finds the atrioventricular valves wide open even though the strength of contraction is weaker. There was little variation in the peak amplitude of the first sound in seven patients with mitral stenosis. Essex and co-workers (170) have indicated the possibilities of recording heart vibrations simultaneously with cinephotography of the valves.

METABOLISM

Detailed studies of the metabolism of the human heart have been carried out by Goodale and co-workers (171) utilizing the method of catheterizing the coronary sinus. With low fasting arterial levels of glucose, lactate and pyruvate, extractions were small or negligible, and with the respiratory quotient of 0.7, the myocardium apparently depended upon fat or other non-carbohydrate sources of energy. In the nonfasting state, the myocardial respiratory quotient was found to vary between 0.86 and 0.93 and significant coronary arteriovenous oxygen differences of glucose, lactate, and pyruvate existed. Results indicated that in heart failure there was no defect in the aerobic oxidative energy production, but rather a failure to convert oxidative energy to effective mechanical work. The utilization of C^{14} -labeled pyruvate and acetate by slices of rat heart has been reported by Pearson and co-workers (172).

HEART FAILURE

Barger and co-workers (173) have reported on a form of progressive right-sided heart failure produced in dogs by avulsion of the tricuspid valve and stenosis of the pulmonary artery. The tricuspid avulsion alone did not produce significant cardiac disability. Three dogs showed the typical picture of congestive heart failure, and studies of the hearts of such animals in the heart-lung preparation indicated that myocardial insufficiency was present. Huckabee and co-workers (174) have produced hypervolemic circulatory failure by infusing dogs with large volumes of fluid. It is suggested that the concept of "inflow load" supplant that of venous pressure as a stimulus to changes in stroke output. It is suggested that the only hemodynamic disturbance constant to all types of heart failure is that the cardiac output is reduced relative to the inflow load. Page (175) has pointed out the probable importance of impairment of the heart in the late stage of shock. Changes in vascular reactivity are important in the irreversibility of shock and the heart participates in the loss of responsiveness. Fishman and co-workers (176), in studies of experimental pericarditis, have found that venous pressure increases without decreased cardiac output or increased blood volume. The edema was related to increased hydrostatic pressure plus increased retention of sodium and water which occurred despite evidence of normal renal plasma flow and glomerular filtration rate. Boucek & Grindlay (177) found different types of circulatory failure related to obstruction to venous inflow to the heart and dependent upon whether the venae cavae or the pulmonary veins were obstructed.

Digitalis.—A very complete and detailed analysis of the energy metabolism in the failing heart and of the metabolic action of cardiac glycosides is available in the review by Wollenberger (178). The integrity of the cardiac muscle fiber would seem to be a prerequisite for the action of cardiac glycosides in that the rate of oxygen utilization is changed by glycosides in intact tissue but not in homogenates. Wollenberger has suggested that the cardiac

lesions caused by administration of digitoxin could be related to the increased oxygen uptake by the cells, and the report of Dearing and co-workers (179) on the increased myocardial necrosis produced by digitalis in hyperthyroid animals seems pertinent to such a suggestion. Saunders and co-workers (180) reported that ouabain had no effect on the rate of dehydrogenation of any substrate in homogenates of rat heart. Despite the lack of effect of the glycosides on the metabolism of homogenates, there is evidence that they might act directly on the contracting mechanism of myocardial fibers. Snellman & Gelotte (181) reported a contamination, apparently a deaminase, which acted on the adenosinetriphosphate during preparation of heart actin and prevented the polymerization of the actin to a great extent. Addition of cardiac glycosides was effective in preventing the effect of the deaminase. Cameron (182) noted that a perfused heart had the same sensitivity to digitoxin despite previous perfusion with various pharmacologic agents and introduced this as evidence that the glycosides acted primarily on the contractile mechanisms of the muscle cell. La Barre & Gengoux (183) have found evidence that various glycosides differ in their rate of removal from a perfusing fluid. Evidence indicated that digitoxin formed a rather stable compound with serum proteins, with inactivation and slowing of its removal from the blood by the heart. This phenomenon did not occur with the more rapidly acting strophanthin and convallatoxin. Studies which might be related to these phenomena have been reported by Walton and co-workers (184) who noted that the changes in contractile force developed most rapidly with thevetin and less rapidly with digitoxin. The experiments were performed both on open-chest animals and on animals which had previously had strain gauges stitched directly on the right ventricle. Salter and co-workers (185) found an inotropic synergism of cardiac glucoside and calcium in the frog's heart, which followed a simple linear function. The investigations (186) have been applied to the detection of cardiac glucosides added to human serum. Loubatières and co-workers (187), using the papillary heart muscle from a recently guillotined man, observed that the various digitalis glycosides augmented the force of isometric contraction. Harvey and co-workers (188) studied the early effects of intravenously administered digitoxin on patients with left-sided heart failure and consistently found a significant rise in cardiac output and stroke volume accompanied by a decrease in pulmonary arterial pressure. As these changes were effected without alteration of the right ventricular end diastolic pressure, they could not be ascribed to an action of the drug upon the systemic venous system. Bloomfield and co-workers (189) have also reported evidence that digoxin acted directly upon the myocardium with rise in the cardiac output. Kelly & Bayliss (190) have reported that when digitoxin is given in cardiac failure, the rise in cardiac output is as pronounced in patients with sinus rhythm as in those with atrial fibrillation. The presence or absence of cardiac slowing played no measurable part in producing the hemodynamic improvements following medication with digitalis. Ahmed, McMichael and co-workers (191) have reported that the action of ouabain depended on a direct stimulating action

on the failing myocardium. The total effect of digoxin was found to be similar but the venous pressure tended to fall more in proportion to the change in cardiac output and the fall in venous pressure preceded a "significant" change in cardiac output. Ferrer and associates (192) found that in patients with cor pulmonale having right-sided heart failure, digoxin produced a rise in cardiac output, a reduction in filling pressure but an increase in pulmonary arterial pressure. After recovery from heart failure, a remarkable readjustment occurred, with pulmonary arterial pressures returning to almost normal, which suggested to the authors that in addition to anatomic alterations of the pulmonary vascular bed certain reversible physiologic abnormalities, perhaps anoxia, polycythemia, or distortion of the vascular bed, could have been important factors in the increased pulmonary resistance. Earle and co-workers (193) have suggested that the cardiac glycosides might exert an additional effect on the renal tubular mechanism itself.

Hilton (194) described a polarographic method for the determination of digitoxin both in alcoholic solutions and in blood, and has applied the method (195) to the determination of the blood levels of digitoxin in animals. Friedman and co-workers (196) have studied the rate of renal excretion of digitoxin in normal and cardiac subjects and found the excretion rate to depend on the age of the subject, the method of administration, and the quantity of the drug given. A general discussion of the pharmacology of the digitalis glycosides in regard to the type of effective molecule has been given by Neumann (197).

Other pharmacologic agents.—A powerful inotropic action of epinephrine, norepinephrine, and N-isopropyl-norepinephrine on the mammalian heart muscle has been reported by Garb (198). Barry (199) has reported a strong chronotropic effect of epinephrine on the embryonic chick heart before innervation has occurred. Graham (200) has reported that in the isolated rabbit atrium, low concentrations of acetylcholine may cause a transient stimulation while higher concentrations result in inhibition. A relative lack of potassium causes doses of acetylcholine, previously inhibitory, to stimulate. Nalefski and co-workers (201), in reporting studies on the experimental administration of barium chloride, reached the conclusion that this was a dangerous drug unpredictable in its actions. Clinical studies on the veratrum alkaloids have been reported by Meilman & Krayner (202), and the vasodepressor reflex pathway involved in the response to these alkaloids has been reviewed. It is suggested that the existence of the receptor mechanism in the left ventricle leading to hypotension might have some role in the profound fall in arterial pressure attending myocardial infarction. The decreased heart rate after protoveratrine could be annulled by atropine without, as a rule, abolishing the vasodepressor effect. The inhibition of the cardioaccelerator action of epinephrine and of norepinephrine by the veratrum alkaloids has been reported by Krayner and co-workers (203, 204, 205). Aviado and co-workers (206) reported that injections of veratridine into the coronary arteries caused a reflex bradycardia and vasodilatation as did injections into the region of the carotid body.

Dihydroergocornine was found by Freis and co-workers (207) to inhibit or abolish the vasopressor response to the Valsalva procedure, upright tilting, and the cold pressor test. The electrocardiographic changes progressing through intraventricular block and ultimately ventricular fibrillation caused by the intravenous administration of procaine have been reported by Long and co-workers (208). Doak & Selke (209) mentioned the very slight electrocardiographic changes that were observed in man when 1 gm. of procaine was given in physiologic saline solution over a period of one to three hours.

DiPalma & Schults (210) have reviewed the nature and value of the various antifibrillatory drugs. The effectiveness of quinidine, procaine, and diethylaminoethanol in the treatment of specific types of arrhythmias is stressed. Alpha fagarine, while a potent drug, had the dangerous tendency to initiate ventricular ectopic beats. DiPalma and co-workers (211, 212) studied a series of tertiary amines related pharmacologically to alpha fagarine in regard to their ability to raise the threshold of electrically induced atrial fibrillation in cats. Carr and co-workers (213), having studied the chemical constitutions of the various hydrocarbons and their effect on cardiac automaticity, have reported a distinct diminution in the degree of myocardial sensitization appearing to be associated with the presence of unsaturation in the molecule. The effect of dibenamine was studied on the heart-lung preparation, isolated rabbit atrium, and the dog's atrium in flutter by Acheson and co-workers (214). The protection against cyclopropane-epinephrine irregularities lasted for one and a half to five days. The high degree of protection given by dibenamine against arrhythmias induced by epinephrine injected intravenously in dogs anesthetized with cyclopropane has been reported also by McMillen and co-workers (215). Stutzman and co-workers (216) have reported that methoxamine does not increase the irritability of the cyclopropane-sensitized heart and is a safe pressor agent to use under any type of anesthesia. Moe and co-workers (217) have reported that cyclopropane will decrease the cardiac work capacity in both the heart-lung preparation and the intact animal.

Further work on the cardiac effects of variations in the concentration of quinidine in the blood has been reported by Sokolow & Edgar (218) and by Kalmansohn & Sampson (219). Orias and co-workers (220) have given anti-histaminic drugs in large doses intravenously, and one of the main effects was a constant depressant action on conduction in the heart. Ruskin & Johnson (221) found that British Anti-Lewisite, ascorbic acid, and thiamine had a protective and therapeutic effect against the conduction and cardiotoxic effects of mercury diuretics in the isolated rabbit heart. Thiomerin was found to be markedly innocuous from the cardiotoxic standpoint.

PULMONARY CIRCULATION AND THE HEART

Haddy and co-workers (222) have studied the pulmonary venous and arterial pressures with other variables in the anesthetized dog by the catheter technique. A significant positive correlation was found between the mean pulmonary venous pressure and the cardiac index. Although the mean systemic venous pressure was higher in dogs with high cardiac indices, the

difference was not significant. Campbell and co-workers (223) found that increased intracranial pressure was followed by pulmonary edema when there was a low cardiac output and bradycardia. Increases in pulmonary venous pressure were adequate to explain the origin of the edema without recourse to other theories. Heart volumes were not measured and they did not deign to mention any vagotonic, negative inotropic theory. Paine and co-workers (224) found that experimental pulmonary edema could be correlated with an increased pulmonary lymph flow. Their investigations were interpreted as indicating that the edema could be explained on a hydrostatic basis alone and that Starling's principle applied to the pulmonary as well as to the systemic circulation. Pulmonary edema observed consequent to prolonged inspiratory or expiratory airway resistance in the dog was found by Haddy and co-workers (225) to be associated with significant elevation of pulmonary venous pressure adequate to explain the pulmonary edema. The anomalies of venous return to the heart, including that of pulmonary arteriovenous fistula and anomalous pulmonary venous drainage, were discussed by Friedlich and co-workers (226). In four cases of pulmonary arteriovenous fistula, the cardiac output was normal. A study of the pulmonary hypertension in valvular heart disease has been reported by Borden and co-workers (227). In mitral stenosis the pulmonary arterial pressure was often markedly elevated, and the degree of increase correlated well with the disability of the patient. The dissociation between the pulmonary hypertension and evidence of pulmonary congestion strongly suggested an increase in vascular resistance of an anatomic type. Lagerlöf and co-workers (228), using dye dilution methods, found no consistent difference in the pulmonary blood volume in different stages of congestive heart failure, which agreed with the findings of Borden and co-workers (229) in patients with mitral stenosis. The latter authors mentioned that the increased circulatory volume between the pulmonary artery and systemic small arteries found by them in left ventricular failure could be due to increase in the left ventricular blood. The mean blood volume in this region in normal subjects was found to be 1,160 cc. by Ebert and co-workers (230). In emphysema, Gillanders (231) has found that circulation times were rapid, though the venous pressure was significantly higher than normal. Cournand and co-workers (232) studied the pulmonary circulation following pneumonectomy and reported that mild pulmonary hypertension develops during the course of mild exercise. With strenuous exertion very high pulmonary pressures were sometimes obtained. Very high pulmonary arterial (intrathoracic) pressures during coughing have been reported by McCann and co-workers (233), and attention is called to a syncopal reaction that may occur in susceptible individuals. The possibility of additional spasm of the pulmonary artery with coughing in these patients was considered but could not be proved.

CONGENITAL HEART DISEASE

Considerable attention has continued to be directed toward the intra-atrial pressures. There exists a definite lack of agreement on the factors re-

sponsible for interatrial shunts when the atrial septum is defective. Little (234) carried out a careful study on the volume elastic properties of the right and left atria of dogs' hearts, and the volume elasticity curves plotted for the right and left atrial systems showed that for equal volume increments the right atrial system was more distensible than the left. With his associates (235) he has stated that the *in vivo* observations of the pressures, the atrial volume elasticity measurements, and experiments with a physical model "prove" that the left to right pressure gradient between the atria in hearts with atrial septal defects depends upon the lesser distensibility of the left atrium and increase in right ventricular output. Opdyke & Brecher (236) have published a careful study of the hemodynamics of the interatrial septal defect in the dog with the chest closed and noted that while the interatrial gradient became less with decreasing intrathoracic pressure (inspiration), it was seldom of such magnitude that the gradient was reversed. Hull (237) published a theoretical analysis of the cause and effects of flow through defects of the atrial septum and concluded that interatrial shunt was due to the differences in the normal anatomic features of the atrioventricular orifices and the difference in thickness and shape of the two ventricles. Hickam (238) has emphasized the large flows of pulmonary blood that could be maintained with a small pressure gradient in patients with atrial septal defects. Dow & Dexter (239) wrote that the right ventricle must be more readily distensible than the left and that the interatrial shunt is due, at least in part, to the greater filling of the more distensible ventricle from a common pressure source. With large septal defects, left and right atrial pressures were found to be equal. The mean capillary pressures obtained by wedging a catheter into a branch of the pulmonary arterial system are claimed by Dow & Gorlin (240) to reflect left atrial mean pressures accurately. Lagerlöf & Werkö (241) have used measurements of this type as indicative of mean pulmonary venous pressure. Hamilton and co-workers (242) have reported detailed studies on a patient with congenital heart disease who had severe cyanotic episodes. The intracardiac shunt varied from 0 to 100 per cent as the arterial pressure fell from 165 systolic and 110 diastolic to 65 systolic and 30 diastolic. The uptake of oxygen in the lungs apparently ceased for as long as two minutes during the hypotensive periods. The saturations of mixed venous blood and of arterial blood came to the same very low figure. Graf & Mannheimer (243) have found that children with cyanotic heart disease show an even higher tolerance to breathing a low percentage of oxygen than do healthy children. Burchell and co-workers (244) have also noted the ability of some individuals with cyanotic congenital heart disease to withstand breathing of low oxygen mixtures exceptionally well, even while exercising. The possibility that increasing hypoxia might cause increased pulmonary resistance as a vicious cycle was not supported by their data.

Studies on the cardiodynamics of experimental interventricular communications are reported by Hawley and co-workers (245). An asynchronicity of the left ventricular ejection was reported, with the aorta receiving its portion

of the stroke volume earlier than that portion passing through the shunt. Part of the evidence for their conclusion was the presence of a mid or late systolic vibration appearing on the pressure tracing from the pulmonary artery. In four clinical cases of ventricular septal defect, it was emphasized that the murmur was also midsystolic.

Extensive physiologic data has accumulated in the cardiac catheterization studies which have been directed to the proper diagnosis of congenital heart lesions. Reference may be made to the monographs by Cournand, Baldwin & Himmelstein (246), and to that edited by Mannheimer (247). Reports of extensive investigations are also to be found elsewhere (248). An incomplete list of articles published in the year of this review pertaining to cardiac catheterization in the diagnosis of congenital heart disease includes those of Dexter (249), LaBree and co-workers (250), Holling & Zak (251), Chapman and co-workers (252), and Burchell & Wood (253).

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RESPIRATION

BY JOHN S. GRAY AND FRED S. GRODINS

Northwestern University Medical School, Chicago, Illinois

Because of the large number of articles bearing on respiration, the reviewers have chosen to exclude all articles published in abstract form. These ordinarily are eventually published in full and thus become available to future reviews of this series. Also, the subjects of internal respiration, pulmonary circulation, and the results of the application of pulmonary function tests in clinical disease have been excluded. The reader's attention, however, is directed to the current volume of *Methods in Medical Research* (1) of which nearly 200 pages are devoted to pulmonary function tests.

MECHANICS OF PULMONARY RESPIRATION

Lung volumes.—Osher (2) has shown that the small reduction in vital capacity which results from tilting from the erect to the supine position is linearly related to the reduction of the vertical hydrostatic pressure column. Brozek *et al.* (3) have reported that the minor reduction in residual volume produced by submersion under water can contribute less than 1 per cent error to the estimation of body fat from specific gravities in air and water. Fleisch & Lehner (4) using a plethysmographic method have reported the respiratory mid-position (midway between inspiration and expiration) to be increased on an average of 360 cc. during the hyperpnea of exercise, but only 140 cc. during an equivalent hyperpnea due to carbon dioxide inhalation.

Pulmonary ventilation.—Bucher (5) has reported that in etherized animals of six species ranging from mice to men, the ventilation is related to surface area, but tidal volume and residual volume to body weight. In this connection, Tanner (6) has discussed certain fallacies in the indiscriminate use of per weight and per surface area standards; of the examples he discusses, the basal metabolism appears least objectionable. Cross (7) devised a body plethysmograph suitable for measuring ventilation in new born babies and obtained an average ventilation of 589 cc. per min. and an average respiratory frequency of 28.6 per min. Loeschke (8) has reported the resting ventilation per sq. m. in pregnant women to be double the norm and the increase following the inhalation of pure oxygen to be exaggerated. Müller & Bastert (9) have devised a spirometer with minimal resistance and inertia for determining the maximum breathing capacity (by voluntary hyperventilation). Average values of 178 and 118 l. per min. were obtained in three male and three female subjects, which are perfectly normal values for the standard Benedict-Roth metabolimeter. With a dry gas meter of high resistance they obtained values approximately one third less.

The pneumotachogram.—The problem of devising meaningful and objective methods of interpreting the curves of instantaneous respiratory flow

velocities which are provided in the pneumotachogram (PTG) seems no nearer solution. No two respiratory cycles yield identical curves with respect to both shape and dimensions. The early workers resorted to dimensionless ratios as indices of the shape characteristics of the tracings, but present workers appear to be abandoning this practice. But one would expect that transformation of the tracings to a completely non-dimensional form should be the first step in analyzing the significance of their shape. Since the latter is essentially a reflection of muscular, elastic, viscous (both air and tissues), and inertial forces, a deduction from the PTG and simultaneous pressure curves of the coefficients for these forces should constitute the goal of interpreting the PTG.

Proctor & Hardy (10) describe the PTG obtained at rest, following hyperventilation, in exercise, with maximum respiratory effort and with added external resistance. Specht *et al.* (11, 12) present PTG data obtained at rest and in exercise at ground level and 30,000 ft. and with helium-oxygen mixtures at ground level. Their recording instrument (13) lacks linear calibration and sensitivity at low flow velocities, which may account for their obtaining normal end-expiratory and even end-inspiratory pauses. Cain & Otis (14) have made a more extensive analysis of the effects of adding external resistance. They found expiration to become active when the elastic energy fell short of requirements for overcoming expiratory resistance.

Otis & Bembower (15) simultaneously recorded flow velocities and alveolar pressures (by the transient obstruction method) and thus established an average pressure-flow relationship in twenty normal subjects breathing air:

$$P(\text{cm. H}_2\text{O}) = 0.0275 V + 0.00306 V^2 (\text{l per min.}).$$

According to theory, on breathing helium-oxygen mixtures having nearly the same viscosity, but only one third the density of air, the coefficient of the first term, representing laminar flow, should remain unchanged, but that of the second, representing turbulent flow, should be reduced to one third. With these restrictions, an equation was fitted to experimental data on breathing helium-oxygen mixtures and the results considered as conforming to theory. A re-fitting of the experimental data without these restrictions by the reviewers yielded coefficients of 0.0375 and 0.000144 for air-breathing and 0.0265 and 0.000105 for helium-oxygen breathing, which are in poor agreement with theory, presumably because of the complicated geometry of the respiratory passages.

Absorption.—Courtice & Simmonds have investigated the rate of absorption of saline and plasma from the lungs (16) and from the pleural cavity (17). From both, protein absorption is by way of the lymphatics, and accelerated by respiratory movements, but more rapid from the pleura than from the alveoli. Cooray (18) has demonstrated a specialized area of the lower mediastinal pleura which is responsible for the absorption of particulate matter from the pleural cavity and which localizes such material as a protective function.

Gas mixing in the lungs.—Intrapulmonary gas mixing has been studied by several investigators (19 to 23) all of whom have attempted to define some sort of measure of ventilatory or mixing efficiency. Nitrogen elimination curves obtained during the breathing of pure oxygen have been utilized by Miller *et al.* (19) and by Robertson, Siri & Jones (20). The former employed a mass spectrometer to follow the concentration of expired nitrogen and defined the "nitrogen clearance volume" as the volume of oxygen inspired during the time required for the expired nitrogen concentration to reach 1 per cent. In five normal subjects, these clearance volumes were consistent within subjects and ranged from 16 to 33 l. between subjects. In three emphysematous patients, the values ranged from 116 to 160 l.

Robertson, Siri & Jones (20) defined an index of ventilatory efficiency based on nitrogen turnover rates. Assuming the lungs to consist of volumes connected in series, differential equations describing such a system were formulated and applied to the nitrogen eliminated in expired air during oxygen breathing. The total nitrogen elimination curve was first adjusted to represent the lung component alone by subtracting a correction representing tissue elimination. The resulting curve was then partitioned into three exponential components each representing different fractions of the total lung volume, and each characterized by a different nitrogen turnover rate. An overall "effective turnover rate" was then obtained by averaging the reciprocals of the three individual rates weighted according to the fraction of the total lung volume represented. This effective rate was finally divided by the maximum turnover rate (i.e., ventilation/functional residual volume) to obtain a figure representing the efficiency of ventilation. The latter is a measure of non-homogeneity of the entire respiratory tree, and as such it is reduced below unity by the normal dead space and by any uneven ventilation. Its average value in 18 normal subjects was 0.57. It was not significantly altered by changes in ventilation induced voluntarily or by exercise.

The same laboratory (24) has reported studies on the uptake and elimination of radiokrypton by the tissues of the hand, in which the tissue saturation and desaturation curves are also partitioned into three simple exponential components, representing parallel compartments.

Another index of mixing efficiency has been defined by Bates & Christie (21) who employed a constant volume rebreathing technique with helium as the reference gas. On the basis of a model lung-spirometer system in which complete mixing was assumed between each transfer, an equation was derived expressing the number of complete respirations required to produce 90 per cent mixing as a function of the initial spirometer volume, the functional residual volume, and the tidal volume. An "index of mixing efficiency" was then defined as the ratio (expressed as a percentage) of this theoretical number to the observed number of breaths. The average value of the index was 68 per cent in 27 normal subjects and 25 per cent in 20 patients with emphysema.

Finally, intrapulmonary mixing has been studied by continuous analysis

of the first expiration following an abrupt shift in the composition of the inspired gas. Using his gas-discharge tube nitrogen analyzer, Lilly (22) has followed the changes in nitrogen concentration of expired air following a shift in the inspired gas from pure oxygen to air. The curve so obtained shows three phases: (a) a sloping water vapor plateau curving downward into (b) a phase of rapidly falling nitrogen concentration which slowly curves into (c) a sloping linear final plateau. The first two phases are regarded as representing flushing of the dead space and the author somewhat arbitrarily defines a "kinetic dead space" as the volume from the beginning of expiration to the point at which the nitrogen percentage drops 90 per cent of the way to the value obtained by extrapolating the final linear plateau back to zero volume. The size of this space varied from 170 to 250 cc. in five subjects. The departure of the first two phases from an ideal "staircase" curve was attributed to the presence of non-uniform velocity profiles and fore and back mixing. The negative slope of the final plateau was attributed to uneven ventilation. Accordingly, an "index of mixing efficiency" was defined as the slope of the final linear mixed gas plateau, and its value in a single subject was -1.75 per cent nitrogen per liter of expired volume. The author eliminated the possibility of nitrogen diffusion into the blood contributing significantly to the final slope but did not consider the possibilities of a changing RQ or diminishing dead space contamination.

Using the same type of nitrogen analyzer, Fowler (23) has described the expired nitrogen curve following the reverse shift in composition of the inspired gas from air to pure oxygen. His curves also showed three phases and were essentially mirror images of Lilly's. Fowler eliminated diminishing dead space contamination, diffusion of nitrogen from the blood, and a changing RQ as significant contributors to the slope of the final plateau and, like Lilly, regarded the latter as evidence of uneven ventilation. Accordingly, he proposed as a measure of mixing efficiency a so-called "uniformity index" which represents the ratio of two dilution indices taken at two different points along the final plateau. The distance between the particular points chosen in terms of volume of expired gas may vary, so that the index varies accordingly. If it is true that the sloping final plateau is due to uneven ventilation, and that it is linear as claimed by both Lilly and Fowler, it would appear that Lilly's index of mixing efficiency based on the slope is a more valid measure than Fowler's uniformity index which may be varied arbitrarily and independently of the slope. Fowler considered his results to favor a "sequential" type of uneven ventilation rather than the "layering" apparently favored by Lilly.

The interpretation of the sloping final plateau as evidence of uneven ventilation has been questioned by Armitage & Arnott (25). These authors concluded, on the basis of their own experiments on fractional analysis of expired air, that this phenomenon was due simply to a diminishing contamination by dead space gas and did not indicate uneven ventilation. Calculation of the volume of dead space gas required to produce the observed

changes in the concentration of expired reference gas (helium in this case) gave reasonable figures, i.e., an average of 215 cc. in seven experiments. However, similar calculations applied to Lilly's data by the reviewers, and to Fowler's data by Fowler himself gave much higher dead space volumes approximating 600 cc. The reasons for the discrepancy between these two sets of experiments remain to be determined.

Dead space and alveolar gas tensions.—A method for measuring dead space has been described (26) in which a known volume of hydrogen is inspired and the quantity expired is measured. It is assumed that if the volume inspired is less than the dead space, all will be recovered, whereas if the inspired volume exceeds the dead space, only a part will be recovered. If this is true, the "knee" in the curve obtained by plotting inspired against expired volume should indicate the dead space volume. The method gave average values of 136 cc. during normal quiet breathing, 176 cc. during voluntary deep breathing, and 128 cc. during carbon dioxide hyperpnea. The authors explained the latter result as due to the special ability of carbon dioxide to transmute conducting tissue to exchanging tissue. A more likely explanation is that the method is invalid since it assumes a uniform velocity profile of the flowing gases and ignores the influence of changing flow patterns.

Bateman (27) has reported a unique procedure for measuring both effective dead space and alveolar $p\text{CO}_2$. He rearranged the Bohr equation to express tidal volume as a function of the volume of carbon dioxide eliminated per breath. The equation so obtained was linear in form with an intercept equal to the effective dead space and a slope equal to the reciprocal of the effective alveolar $p\text{CO}_2$. During exercise and recovery, plots of tidal volume against carbon dioxide output per breath were linear, indicating that both the effective dead space and the effective alveolar $p\text{CO}_2$ remained constant under these conditions, and thus providing a simple method for measuring them both. Confirmation of these observations is important since they have a number of significant implications.

A new method of alveolar sampling designed to avoid dead space contamination and eliminate interference with the normal respiratory pattern has been described (28, 29). The device automatically flushes the mouth by suction before taking a sample at the end of a normal expiration. The method was primarily developed for use in the determination of cardiac output by the indirect Fick method, and some results of this application have been reported (30, 31). Of interest in this connection is the report of Armitage & Arnott (32) indicating that oxygen consumption may be doubled during one deep breath and increased 50 per cent over five deep breaths, presumably due to increased pulmonary blood flow. The implication is that deep breathing should be avoided when cardiac output is measured by indirect Fick methods. Evidence that some alveolar air still remains in the mouth at the end of a normal or deep inspiration has been obtained by Forssander (33).

Winterstein (34) compared the changes in alveolar $p\text{CO}_2$ and total venti-

lation on going from sea level to an altitude of 5,900 ft., and concluded that the fall in alveolar $p\text{CO}_2$ was not dependent on increased ventilation alone, but also on improved diffusion of carbon dioxide at the reduced barometric pressure. He also stated that since there is no invariable proportionality between alveolar $p\text{CO}_2$ and ventilation, it is impossible to calculate the latter from the former. It should be pointed out that no one has claimed an invariable proportionality between alveolar $p\text{CO}_2$ and total ventilation as Winterstein apparently assumes, nor even between alveolar $p\text{CO}_2$ and alveolar ventilation, since changes in oxygen consumption and/or RQ alter the latter relationship. Thus, Winterstein's observations might be explained by an altered relationship between alveolar and total ventilation, a change in oxygen consumption, or a change in RQ . Since the latter two were not measured, none of these possibilities can be eliminated.

Rahn (35) has defined on theoretical grounds the composition of an ideal mean alveolar air. The definition is based upon the principle that if mixed venous blood of known composition gives off carbon dioxide and removes oxygen from tracheal air of known composition, equilibrium will be reached at only one possible value of $p\text{CO}_2$ and $p\text{O}_2$ for any given RQ , and each RQ corresponds to a single possible ventilation-perfusion ratio. Stated a little differently in terms of the blood-lung exchange system, the independent variables may be regarded as the compositions of venous blood and tracheal air, and the ventilation perfusion ratio. Any given combination of these defines a single possible RQ and alveolar composition. Evidence is presented to indicate that the automatic sampling of alveolar air from the end of a normal expiration gives $p\text{CO}_2$ values very close to the theoretical mean, whereas Haldane-Priestly end-expiratory samples give high results.

Since the theoretical definition assumed a uniform ventilation-perfusion ratio throughout the lung (and this is probably unlikely), the author has examined the influence of variation in this ratio according to an arbitrarily assumed distribution. The mean alveolar air resulting from such a variation did not differ significantly from the theoretical mean, but the $p\text{O}_2$ of arterial blood was reduced, giving rise to an alveolar-arterial gradient for oxygen.

REGULATION OF RESPIRATION

Respiratory centers and cycle control.—The currently accepted view that the medullary respiratory center is not inherently periodic but is dependent for its rhythmic activity upon the vagal and pneumotaxic circuits has been seriously questioned by Hoff & Breckenridge (36, 37). Noting that this hypothesis has been based solely upon the observation that animals with transections below the upper pons pass into a state of apneusis or inspiratory spasm when the vagi are cut, these authors have reinvestigated this phenomenon in both the dog (36) and the cat (37). The results in both species were similar and indicated that apneusis was neither permanent nor total but instead diminished and disappeared with the return of periodic breathing as the preparation deteriorated. Moreover, if the medulla was more com-

pletely denervated either by section of the auditory and glossopharyngeal nerves or denervation of the carotid bodies in the dog, or by high medullary transection in both species, all traces of apneusis disappeared and a normal rhythmic breathing remained. The authors concluded from these observations that apneusis represents a phenomenon which can be clearly dissociated by appropriate transections from rhythmic respiration of medullary origin, and that the medullary respiratory center is inherently periodic. They attribute the growth of the concept of apneusis as a permanent inspiratory spasm to the use of animals in such poor condition that the initial apneustic period proved fatal, to the technique of temporary vagal blocking permitting reactivation of the vagi so that, in effect, no animals were carried beyond the initial period of apneusis, and finally to the fact that most preparations involved ligation of the carotids which favors prolongation of apneusis. Nevertheless, however, the facts that apneusis disappeared as the preparations deteriorated, or following transection below the striae acousticae, were not unknown to earlier investigators, but a different interpretation was made of them.

The location of the vagal stretch receptors in the lungs has been studied (38) and it was concluded that at least 60 per cent of the total are located in the visceral pleura itself or its immediate vicinity. Wyss & Rivkine (39) have identified three types of afferent fibers in the vagi which participate in respiratory reflexes. The slowest fibers stimulated inspiration and were believed to originate in deflation receptors; intermediate fibers inhibited inspiration and were believed to originate in inflation receptors. From somewhat similar studies, Woldring (40) agrees with Wyss that the most marked inspiratory inhibition is produced by high frequency stimulation of the vagi, but differs from him in regarding low frequency stimulation as also inhibiting inspiration. The vagi are necessary for the tachypnea produced by pulmonary starch emboli in the cat (41). The results of Eichenberger (42) indicate that the ventilatory response to carbon dioxide is much reduced after vagotomy in the rabbit. This is of interest, since the vagi are generally regarded as regulators of respiratory pattern but not of minute volume.

Respiratory responses to electrical stimulation of the cerebral cortex have been studied in man (43), monkey (44), and the dog and cat (45).

Control of ventilation.—Reports of the past year dealing with the regulation of pulmonary ventilation illustrate all the points of argument and confusion which have so long characterized this field. All these perennial difficulties are on the interpretational level; there neither is nor has been any real disagreement on the observational level. Yet no amount of repetition of experiments which continue to yield the same data can ever clarify interpretational confusion.

A short monograph (46) has appeared which gives a more complete presentation of the multiple factor theory of ventilation control, although not in full mathematical detail. According to this theory, ventilation is controlled by many individual stimuli, including among others the three chemical

agents, $p\text{CO}_2$, pH, and $p\text{O}_2$. Each stimulus contributes its own partial effect, the algebraic sum of which represents the actual ventilation. The three chemical agents also constitute the feedback control channel, for nearly every change in ventilation affects their blood levels. The theory accounts quantitatively for the behavior of ventilation in the steady state of carbon dioxide inhalation, anoxia, metabolic acidosis, and alkalosis singly and in combination. Both $p\text{CO}_2$ and pH are considered primary stimuli and the partial effects of each have been quantified. An exact definition is provided for the partial sensitivities of the control apparatus to various stimuli, thus transferring this concept from the realm of language to that of experiment. The assumption of universal dissociation of arterial and tissue concentrations of stimuli become unnecessary, so that this mechanism can be reserved for transient states where its behavior can be analyzed. Above all, a means is provided for distinguishing between partial ventilatory responses which are additive and total responses which are rarely additive because of intervention of the whole feedback control system.

Loeschke (47) has independently arrived at the fundamental principles of the multiple factor theory. He points out that the concept of changing irritability of the respiratory centers has been used as a word rather than as a physiological mechanism and that there is no possible way of deciding which of two agents is a stimulus and which a sensitizer. He also indicates the necessity of limiting to well-defined states the concept of dissociation of arterial and tissue concentrations. Finally he points out that several respiratory stimuli must be concerned and that the published evidence, which is usually interpreted as altered sensitivity, actually proves that the effects of the several stimuli must be additive.

Bruce *et al.* (48) have attempted a factor analysis of the transient respiratory responses of dogs to fatal anoxia. The application of multiple curvilinear correlation methods yielded an unsatisfactory equation because of the highly variable unsteady states and because only anoxia, with its restricted patterns of relationships between the chemical agents, was considered. For the latter reason, $p\text{CO}_2$ appeared as a stimulus negatively related to ventilation. Because of the severe anoxia both respiratory alkalosis and acidosis, and metabolic acidosis occurred, thus providing several patterns of relationship between pH and $p\text{CO}_2$, which the multiple correlation technique is completely unable to handle. A Thurstone factor analysis revealed that both pH and $p\text{CO}_2$ were stimuli, and, as is well known, that their concentrations are not independent of one another.

Winterstein (49) has also condemned the uncritical use of the irritability concept as a linguistic device rather than a physiological one. He gives a full presentation of his modified "reaction" theory which attributes the control of breathing to the intracellular pH's of the medullary centers and arterial chemoreceptors, which pH's therefore must be dissociated from that of the blood. The quantitative discrepancy between the ventilatory responses to carbon dioxide and fixed acids when the blood pH's are identical, is attrib-

uted to the depressing effects of fixed acid anions, and to a stimulatory effect of inhaled carbon dioxide acting in the lungs. The hyperventilation of anoxia, which is accompanied by an alkalemia, is attributed to an endogenous fixed acidosis within the chemoreceptor cells. But if anoxia produces an acidosis here, it certainly should in the cells of the respiratory centers, in which case the hyperventilation should occur following chemoreceptor denervation. The hyperpnea of exercise is dismissed as being beyond present understanding.

Hesser (50) has again tried to identify the primary respiratory stimulus by comparing responses to carbon dioxide and fixed acids in the transient state. Since he also found that the pH fell in both types of acidosis whereas the $p\text{CO}_2$ changed oppositely in the two, he concluded the pH must be primary; the quantitative discrepancy was ignored. Since in the transient state the venous pH rather than the arterial pH paralleled the ventilation, he concluded that the effective site of action must be intracellular. Such evidence, however, would equally well support a venous, capillary, or tissue fluid site of action. The increase in "irritability" towards $p\text{CO}_2$, claimed by others to occur in metabolic acidosis, he attributes to the fall in blood buffer capacity which allows a greater change in pH per unit change in $p\text{CO}_2$; but the observation demanding explanation is a greater ventilation for a fixed pH value when carbon dioxide is breathed than when a fixed acid is given.

Gollwitzer-Meier (51) reports that chemoreceptor denervation in anesthetized dogs does not affect the response to 3 per cent carbon dioxide, but converts that to 8 per cent oxygen from stimulation to depression progressing to apnea. In both denervated and intact animals the combination of 3 per cent carbon dioxide and 8 per cent oxygen provoked a response greater than the sum of the individual responses. Such potentiating total responses are perfectly possible with additive partial effects in a feedback system. The amazing conclusion was drawn that exogenous hypercapnia (from carbon dioxide inhalation) stimulates respiration, whereas endogenous hypercapnia (from anoxic depression of breathing in the denervated dog) depresses respiration.

Rahn & Otis (52) suggest that the mild anoxia of low altitudes fails to provoke hyperventilation (in spite of increased chemoreceptor nerve activity) because the hematic alkalosis resulting from the fall in oxygen saturation antagonizes the anoxic stimulus. This should settle the arguments concerning the "threshold" for anoxic stimulation. These workers also show that the exaggerated hyperventilation of prolonged (as contrasted to acute) exposure to altitude reaches a steady state in about four days at 9,500 ft., although a longer period may be required at higher altitudes. This acclimatization hyperventilation they attribute, without inquiry into the quantitative aspects, to the withdrawal of alkalemic inhibition which results from renal compensation of the initial alkalosis. A previous analysis of the same data, by one of the reviewers (53) revealed that this mechanism is quantitatively

quite inadequate, and so an increased partial sensitivity to carbon dioxide was proposed. Rahn & Otis refer to an increased carbon dioxide pseudosensitivity (actually sensitivity to both $p\text{CO}_2$ and pH expressed as function of $p\text{CO}_2$ alone) which results from the fall in blood buffer capacity, but this cannot account for the exaggerated hyperventilation which persists when the pH is normal, the $p\text{CO}_2$ reduced, and as they claim, the transient anoxic drive through the chemoreceptors has disappeared.

Habisch (54) and Schäfer (55) have reported that several days' exposure to 3 per cent carbon dioxide results in a gradual reduction of the initial hyperpnea, accompanied by uncertain changes in the pseudosensitivity to carbon dioxide, but with a consistent increase in the carbon dioxide apnea point. Whether these acclimatization phenomena are the result of compensation of the initial respiratory acidosis, or of a reduction in partial sensitivity to carbon dioxide is unknown. Other effects of prolonged carbon dioxide exposure are reported (56 to 59).

Mond (60) discusses the parallel reduction in RQ and venous carbon dioxide content observed in fasted rabbits in the light of respiratory regulation. Roth (61) reports the ventilation during the terminal minute of re-breathing anoxia to be as high at rest as at increasing work levels. Aviado *et al.* (62) suggest the existence of lung chemoreceptors in view of their finding that intravenous (but not intra-arterial) injection or aerosol inhalation of veratridine produces transient apnea which is independent of cardiovascular changes but dependent upon an intact vagus nerve. Schroeder & Blohmke (63) report that an excitatory pressor-reflex may be elicited from the right atrium which predominates over the antagonistic arterial pressor reflex. Richmond (64) finds that caffeine (but not aminophylline) stimulates ventilation by increasing absolute amounts as the level of ventilation is augmented by carbon dioxide inhalation. Neglecting the fact that the responses of a complex feedback control system are not simple, they conclude that caffeine must increase sensitivity to carbon dioxide. Ellis *et al.* (65) report that typhoid vaccine does not affect the ventilatory response to carbon dioxide although they had previously shown that it abolishes thermal panting in heated rabbits. Stacy *et al.* (66) suggest that epinephrine may be a respiratory stimulant concerned in the response to anoxia, since adrenalectomy reduced this response. Hoff *et al.* (67), on the other hand, suggest that epinephrine exerts an inhibitory effect directly on the respiratory centers, since it retains its apneic action after deafferentation of the medulla oblongata. Nickerson *et al.* (68) report that intraperitoneal epinephrine in the rat produces a prompt hypertension which in turn induces a delayed but fatal apnea; artificial respiration restored normal breathing in spite of a persistent hypertension, but by control of the latter all respiratory difficulty could be prevented. Liljestrand (69) failed to confirm earlier claims that antihistaminics specifically depress the respiratory response to carbon dioxide. Anderson *et al.* (70) have demonstrated that periodic breathing (and arterial pressure oscillation) incident to depressed medullary centers is abolished by chemoreceptor denervation.

Grodins (71) has made an analysis of the hyperpnea of exercise in the light of the multiple factor theory. It is shown that the three chemical agents cannot account for the hyperpnea and that some additional stimuli of as yet unidentified nature must be acting in additive fashion. It is also made clear why previous attempts to identify the exercise stimulus or to determine its pathway (reflex or humoral) have necessarily been unsuccessful. Bahnson *et al.* (72) have clearly demonstrated that the so-called "passive" exercise is identical with mild active exercise insofar as oxygen consumption, ventilation, and the ventilation equivalent for oxygen are concerned. Hence, "passive" exercise experiments do not provide a different approach to the hyperpnea of exercise. Asmussen & Nielsen (73) have shown that blood sequestered in the legs after hard work until the ventilation has subsided, will on release provoke a transient hyperpnea reaching a prompt peak of 400 per cent. If pure oxygen is breathed during sequestration and release, the response is slightly diminished. Something more than accumulated carbon dioxide is involved, since the effect of release could not be duplicated by brief carbon dioxide inhalation. These results are interpreted to mean that muscles in heavy work release a humoral agent which is responsible for the accompanying hyperpnea. Further experiments (74) eliminated pyruvate as being the agent in question. Bruce *et al.* (75, 76) have presented extensive data on the transient responses of human subjects to mild exercise.

RESPIRATORY DISTURBANCES

Anoxia.—Grandpierre *et al.* (77) discuss in detail the "paradoxical" responses to the sudden administration of oxygen in anoxia, including the transient apnea, hypotension, bradycardia, neuromuscular irritability, and clouding of consciousness. The effects of moderate altitudes on psychological performance tests (78, 79), acid-base balance (80), glucose tolerance (81, 82), eosinophile count (83), and 17-ketosteroid excretion (84) have been reported. Many of these effects are interpreted in terms of altered adrenal cortical activity. Berger *et al.* (85) found no change in renal plasma flow in normal subjects breathing 14 per cent oxygen, but significant increases in urinary excretion of Na^+ and Cl^- . Franklin *et al.* (86) report that severe anoxia reduces renal cortical blood flow by a neurogenic mechanism. Krienberg *et al.* (87) observed that 6 to 7 per cent oxygen reduced renal blood flow (stromuhr) in dogs and that the effect was increased by including 3 per cent carbon dioxide in the mixture. The surprising conclusion was drawn that acapnia rather than anoxia is responsible for the effect. Christensen & Hastings (88) reported no changes in arterial pH, pCO_2 , or BHCO_3 in unanesthetized rats at 18,000 ft., but that above 27,000 ft. only the pH and BHCO_3 were reduced. There is no explanation for the absence of respiratory alkalosis at the lower altitude nor the failure of respiratory compensation of the metabolic acidosis at the higher altitude. The effects of temperature and humidity (89 to 92) and previous exposure (93) on survival of small animals subjected to acute anoxia have been investigated and interpreted in terms of the rate of metabolism. The finding that the survival time following expo-

sive decompression reaches a minimum fixed value (94), and that the altitude at which this occurs is only slightly higher with oxygen than with air has been analyzed by Luft *et al.* (95) and explained in terms of a critical alveolar oxygen tension which is affected by reversed direction of oxygen exchange. Bowen & Eads (96) find no increase in muscle myoglobin in dogs repeatedly exposed to 18,000 ft. Both rats (97) and rabbits (98) are reported to develop increased vascularity of the brain during acclimatization to altitude.

Carbon dioxide.—Penneys (99) has devised a means of maintaining a constant anoxemia while varying the carbon dioxide content of inspired air, in order to distinguish acapnia from anoxemic effects. In 20 normal subjects he found that acapnia is responsible for the subjective symptoms of anoxia, while anoxemia is responsible for the tachycardia and altered RST segment; both contribute to lowering the T wave. Langley *et al.* (100) found that the inclusion of 9 per cent carbon dioxide in the inspired air prevented the accumulation of liver glycogen which otherwise occurs in rats exposed to 20,000 ft. They conclude that the glycogen accumulation is an acapnia rather than anoxemic effect, but neglect the fact that carbon dioxide effectively corrects anoxemia when added to air. Further evidence that hypercapnia plays a role in oxygen poisoning is provided by Taylor (101) who found that in cats subjected to 4 atmospheres of oxygen pressure, the tissue $p\text{CO}_2$ rose to 400 mm. Hg and that the inclusion of only 23 mm. Hg of carbon dioxide partial pressure in the inspired air hastened the onset of convulsions to its minimal time. Further effects of "diffusion respiration" with its intense hypercapnia on cardiovascular phenomena (102) and the EEG (103) have been reported. Pollock (104) has also reported depression of EEG activity with high percentages of carbon dioxide and in addition an antagonistic action against metrazol and electrical convulsions. Spencer *et al.* (105) subjected lightly anesthetized dogs to percentages of carbon dioxide ranging from 10 to 40 per cent for 45 minutes. In all cases, the respiratory frequency was increased and maintained, but with the higher concentrations the tidal volume soon declined below normal, and anesthesia was maintained by the carbon dioxide alone.

Anesthesia and asphyxia.—Beecher *et al.* (106) made a careful study of the state of acid-base balance in ether anesthesia and contrary to textbook statements found no deviations from normal. A similar study (107) of anesthesia during open chest surgery revealed adequate oxygenation, but severe respiratory acidosis with pH's as low as 7.1 and $p\text{CO}_2$'s as high as 100 mm. Hg. These effects were attributed to the surgical position. In this connection, Sokalchuk *et al.* (108) have investigated various surgical positions from the standpoint of their effects on ventilatory function. No changes were found in blood gases in spinal anesthesia (109) but pre-operative sedation with barbiturates, or morphine and scopolamine, was found to reduce pulmonary ventilation from an average of 10.4 l. per min. (which is high) to 7.8 (which is only normal) (110). Swann & Brucer, in a series of papers (111 to 117), have described in detail the respiratory, cardiovascular, and blood composition

changes in unanesthetized dogs subjected to fatal anoxia and asphyxia induced by oxygen-deficient air, tracheal obstruction, carbon monoxide poisoning, and fresh and salt water drowning.

METHODS

Frank (118) has described a method for preparing dogs with a chronic tracheal fistula for respiratory studies without anesthesia. Bateman *et al.* (119) have described a spirometer having minimal dead space for following the clearance of nitrogen from the lungs. Donald & Christie (120) have devised a recording spirometer which segregates inspired and expired gases. Döbeln (121) describes a valve for separating inspiratory and expiratory flows which has a dead space of 10 cc.

Van Slyke *et al.* (122) have adapted the phenol red method for plasma pH determination to the photometer. Methods are described for the spectrophotometric measurement of blood oxygen (123, 124). The tonometric method of Comroe & Dripps for blood pO_2 has been modified and extended to blood pCO_2 and pN_2 (125). Modifications have been described for measuring pO_2 's of fluids with the platinum electrode (126, 127). Fry (128) has published a description of his simple gas analyzer. The newer physical methods for gas analysis are described and discussed (129 to 131). The second edition of *Medical Physics* (132) contains extensive new material on methods.

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KIDNEY¹

BY EWALD E. SELKURT

*Department of Physiology, School of Medicine, Western
Reserve University, Cleveland, Ohio*

Advances in renal physiology during the period covered by this review have been made mainly in the study of enzymatic processes concerned with tubular transport systems, aided by application of the Warburg manometric technique combined with observation of the rate of transfer of substances by kidney slices. Rapid advancement in the field of renal electrolyte handling has also occurred, aided by the use of the flame photometer. The mechanisms of sodium and potassium clearance by the normal and diseased kidney have received particular attention. In reviewing the literature concerned with renal pathology, one is impressed with the universal attention given to the possibility that the Trueta mechanism (Oxford shunt) may be a basic mechanism in all types of nephropathies. A number of functional studies are reported which test this hypothesis.

GLOMERULAR FILTRATION RATE

Inulin clearance still remains the standard of reference for the measurement of glomerular filtration rate, although this has been questioned by one group. Difficulties of obtaining pure samples of inulin, especially in Europe, and analytical complexities have continued to stimulate the search for other substances whose clearance measures filtration rate. The development of more simplified analytical methods for inulin has in part remedied this situation. Desirability of devising techniques for routine clinical measurement of kidney function has prompted further experimentation with methods either requiring no urine collection or collection without catheterization, and not requiring continued intravenous infusion.

Indirect measurement of the clearance of a substance by the plasma slope method requires that it be excreted solely by the kidney, and that proper time be allowed for equilibration in fluid compartments in the body (1). The clearance then becomes: $C = V_e \times S$, where V_e is the volume of distribution, and S is the slope of the line representing its rate of disappearance from the plasma. Using this method, Houck (2) found the urine clearance/slope clearances ratios for mannitol to average 0.90 in the dog, with negligible extra-renal loss. Robson *et al.* (3) found that inulin did not attain a constant volume of distribution in two hours in human subjects, and devised an improved formula to correct for this phenomenon:

$$C = \frac{b(\log P_1 - \log P_2)}{\log (V_1)_2 - \log (V_1)_1} - b,$$

in which V_1 is the volume of distribution of inulin (amount injected—amount

¹ This review covers approximately the period from June 1, 1949 to June 1, 1950.

excreted/concentration in plasma water). P_1 and P_2 are values obtained from the plasma water inulin-time curve, and the constant b is derived from the equation for the slope of change of V_I . The technique involves a single intravenous injection of inulin, with spontaneous passage of urine between 35 and 120 min. at which time P_1 and P_2 are taken. Voluntary micturition is adequate for computation of the amount excreted when calculating V_I . Comparison of this method with simultaneous urinary clearance yielded excellent agreement. Schwartz, Breed & Maxwell (4) measured inulin and mannitol total plasma clearance by an indirect method in which the rate of constant infusion in mg. per min. is divided by the plasma concentration at the midpoint of the observation period. The total clearance of inulin measured in this manner agreed well with the simultaneous urinary clearance, but that of mannitol was about 17 per cent high, indicating extra-renal loss of mannitol. The mannitol/inulin renal clearance ratio averaged 0.89, confirming the earlier findings of mannitol tubular reabsorption (5, 6).

Robson *et al.* in a later paper review the evidence for the validity of the inulin clearance as a measure of glomerular filtration rate (7). One of the important lines of evidence has been that UV is linearly related to P , beginning at zero. They argue that backward extrapolation by visual inspection of a line drawn to fit fairly high ranges of plasma concentration may obscure small deviations from the point of origin. Using their single injection technique in normals and hypertensives, clearance decreased in a plasma range from 64 to 5 mg. per cent, as might be expected with a substance that is partly reabsorbed. When plotted as a regression line ($UV = aP - b$, where a and b are constants derived by the method of least squares), the line intercepted the abscissa before zero. This was confirmed with constant infusion techniques. Since all projected regression lines finally cut the ordinate at negative values (-2.9 to -14.3 mg. per min.), they assume that inulin is being reabsorbed at this rate, and accordingly does not accurately measure filtration rate in man. If this contention proves to be correct, it should not invalidate the use of inulin clearance at higher plasma levels, since the amount reabsorbed would then be negligible compared to the total amount filtered.

The French have used sodium hyposulfite by the single injection technique as a substitute for inulin for measurement of filtration rate. In a group of normals its clearance fell between 110 to 150 ml. per min., and in the range of 12 to 20 ml. per min. in chronic glomerulo-nephritis (8). Assuming mannitol clearance to be a measure of filtration rate, Lebrun (9) found hyposulfite/mannitol ratios to average 1.03 when plasma concentration was above 12 mg. per cent, but below this level it averaged 1.33. He concluded from this that hyposulfite was in part secreted by the tubular cells. This was confirmed by blocking its secretion with carinamide, under which circumstance the hyposulfite/mannitol ratio averaged 0.956. Nevertheless, the clearance at plasma levels above 20 mg. per cent is accepted as an adequate measure of filtration rate.

When interference by noncreatinine chromogens was avoided by adsorption-elution analytical techniques (263), the endogenous creatinine/inulin clearance ratio was found to average 1.03 (0.82–1.26), and the exogenous creatinine/inulin ratio 1.08 (0.97–1.20) (10). However, in chronic renal insufficiency, the clearance of both endogenous and exogenous creatinine was elevated well above inulin. The clearance of ferrocyanide was found by Berliner *et al.* (11) to average 0.966 of the simultaneous creatinine clearance in dogs, confirming its use as a measure of filtration rate in this animal.

The validity of the use of thiosulfate clearance as a measure of filtration rate is extended to the rat (12), where its clearance is independent of plasma level and averages 0.594 ml. per min. The thiosulfate/inulin ratio averaged 1.03. Strangely, this is not the case in cats, for here the thiosulfate/creatinine ratio varied with the plasma concentration, being close to unity at about 180 mg. per cent and increasing to 2.4 at the lowest plasma levels (13). This interesting evidence of tubular secretion of thiosulfate by the cat kidney has been confirmed by Effersøe (14) in kittens a few weeks old.

TUBULAR FUNCTION

Reabsorption.—With increasing loads of creatine, reabsorption increases proportionally, but at all levels of filtration less is reabsorbed than filtered, and no clear cut T_m could be demonstrated (15). Nevertheless, the mechanism appeared to be reproducible in a given subject. Guanidoacetic acid displayed a similar relationship, but was less efficiently reabsorbed at comparable loads. This substance was blocked by creatine, but the reverse effect could not be demonstrated. This lack of T_m for creatine was confirmed by Zierler *et al.* (16). At higher loads, the ratio of creatine clearance/filtration rate tended to reach constant values ranging from 0.55 to 0.81.

Berliner and his co-workers (17) found that some urate was excreted at all plasma levels and gradually approached T_m , exhibiting a splayed relationship between load and amount reabsorbed. The relationship was reproducible in the same subjects and averaged 15 mg. per min. per 1.73 sq. m. in four subjects. In making their calculations, these workers assumed complete diffusibility of urate.

The clearance of radio-iodine has been found to average 31 ml. per min. in man, suggesting a mechanism of filtration and reabsorption (18). A low "threshold" for iodide is indicated by the fact that at plasma concentrations of 1.6 m.eq. per l. in dogs, the clearance was only 0.05 to 0.79 ml. per min., but when the level was increased to 11 m.eq. per l., the clearance of iodide increased to 8 ml. per min. (19). Salicylate clearance is normally less than 10 per cent of filtration rate, but this low clearance may be due entirely to plasma binding rather than tubular reabsorption (20). Giving sodium bicarbonate increases the clearance, either by influencing plasma binding or by blocking tubular reabsorption.

Beyer, Peck, *et al.* (21, 22) have investigated the mechanism for the renal clearance of carinamide which has been shown to block the tubular

secretion of PAH (*p*-aminohippurate), penicillin, and other substances. Adsorption of this compound and its metabolites to the blood proteins and cells has complicated the analysis of the mechanism, but the final conclusion reached was that this substance was filtered and reabsorbed.

Tubular secretion.—An attempt to measure renal plasma flow by the single injection plasma slope method was made using PAH (23). Slope clearances were found to be consistently too high compared to simultaneous urinary clearances in patients when they were based on the volume of distribution of PAH. However, empirical use of the volume of distribution of mannitol, which has a rapid diffusion coefficient, yielded a plasma slope clearance/urine clearance ratio which averaged 0.91 (0.65–1.08). The probable reason for the failure when based on volume of distribution of PAH is apparent from the work of Barker *et al.* (24), who emphasize that equilibrium is absolutely essential for clearances of this type, and that this takes about two hours.

Recognizing this phenomenon, Robson *et al.* (25) have applied the same rationale used in their method for measuring the inulin clearance by the single injection method, and have developed equations for the measurement of diodrast clearance and Tm_D . The equation for C_D is the same as that used for C_{IN} above, but the equation for Tm_D is more complex:

$$Tm_D = (C' + m) \frac{P_2(V_D)^{\frac{C'+m}{m}} - P_1(V_D)^{\frac{C'+m}{m}}}{(V_D)^{\frac{C'+m}{m}} - (V_D)^{\frac{C'+m}{m}}}$$

where C' is the amount filtered ($FW \cdot C_{IN}$), and V_D is the volume of distribution of diodrast, and the constant m is derived from the equation for the slope of change of V_D taken 25 and 120 min. after injection, and P_1 and P_2 are the plasma concentrations at these times. C_D and Tm_D measured in this manner were found to be in good agreement with simultaneous renal clearances.

Other investigations have tested the concept of Tm as a constant, reproducible index of maximal rate of tubular secretion. Davies & Shock (26) found the day to day variability of the measurement of inulin and diodrast tests to exceed the experimental errors of the method as evidenced by period to period variation. Barclay *et al.* (27) found marked irregularities in diodrast Tm in hypertensives and glomerulonephritics, as well as in normals. Since variations presented a trend when successive periods were averaged, they believed that the results were not due to bladder emptying errors. They established what appeared to be a significant relationship of Tm_D to the plasma iodine level, whereby the Tm tended to decrease with increase in plasma iodine, suggesting a possible toxic action of diodrast iodine on the tubular cells.

PAH has been shown by McDonald *et al.* (28) to produce vasomotor side-effects which influence renal clearances in humans. Filtration rate de-

creased from 94 to 82 ml. per min. when PAH plasma levels were raised from low to T_m levels, but renal plasma flow (measured by the Fick principle by catheterization of the renal vein) actually increased, associated with signs of increased cardiac output (increase in heart rate, systolic, diastolic, and pulse pressure). C_{PAH} is higher than C_{CR} in cats at low plasma levels, and T_m is reached above 10 mg. per cent (2 to 4 mg. per min., or to 20 to 30 mg. per min. per 100 ml. glomerular filtrate), according to Eggleton & Habib (29). However, when the plasma concentration was elevated above 100 mg. per cent, T_m was depressed, so that finally the total amount excreted in the urine was less than the calculated filtered moiety, suggesting tubular reabsorption of PAH. Speculation is raised as to whether the mechanism for PAH handling in the cat involves both secretion and reabsorption, or whether this represents a toxic manifestation.

Competitive renal tubular mechanisms.—Numerous examples of competition for transfer systems, both secretory and reabsorptive exist (30). Another interesting example is disclosed by Riggs between the halides, iodide, and chloride (19). Carinamide, itself reabsorbed, has been shown to inhibit the tubular secretion of phenol red (31), *p*-amino-salicylic acid (32), and to decrease the excretion of 17-ketosteroids (33). The view is nevertheless taken by Beyer (34) that carinamide blocks some distinct aspect of tubular transfer rather than tubular secretion as a whole, based on the finding that *N*'-methylnicotinamide secretion is not blocked by this substance, nor do PAH or other nicotinic acid derivatives compete for its transfer.

Earlier examples of nonspecific competition (PAH by glucose) (35, 36) should be re-evaluated in the light of recent findings. Baldwin *et al.* (37) found that when PAH was mixed with 5 per cent glucose in the infusion flask, a reaction product was formed which has a lower clearance than normal PAH. This is hydrolyzed back to its original form during chemical analysis, yielding higher concentrations of free PAH in the plasma which result in apparent depression of PAH extraction and C_{PAH} .

METABOLIC ASPECTS OF TUBULAR FUNCTION

Oxygen consumption and renal work.—By means of renal vein catheterization, Cargill & Hickam (38) found that oxygen consumption is 16.0 ml. per min. (S.D. ± 2.9) by normal human kidneys, and oxygen extraction is 1.42 vol. per cent (S.D. ± 0.25). Decrease in filtration rate and renal blood flow in essential hypertension, nephrosclerosis, and chronic nephritis is accompanied by comparable decreases in oxygen consumption, and by slight increases in oxygen extraction. Decreased oxygen consumption may reflect reduction in tubular mass, or may be the result of decreased work caused by reduction in the filtered load. The last conclusion is supported by the marked reduction in oxygen consumption in acute glomerulonephritis (7.3 ml. per min.) where the major alteration is decrease in filtration rate. Clark & Barker (39) found renal oxygen utilization of 18.3 ml. per min. in

normal human subjects. Saturation of the PAH transfer mechanism, water diuresis, and mannitol diuresis caused surprisingly small variations in amount of oxygen utilized. Rapoport *et al.* (40, 40a) compared the amount of thermodynamic work in the resting kidney of hydropenic man with that subjected to various types of osmotic diuretics. For resting kidneys, the average was 0.63 cal. per min. per 1.73 sq. m. The "calculated ideal osmotic work" rose to a maximum of 4 cal. per min. during maximal osmotic loading. Theoretical considerations, based on normal oxygen consumption of the human kidneys, indicate that even with forced osmotic diuresis the thermodynamic work accounts for only about 8 per cent of the total metabolic demands of the kidneys.

Enzymatic processes concerned with renal tubular transfer.—Application of the Warburg manometric technique combined with observations on the rate of accumulation in kidney slices of substances known to be secreted by tubular cells (phenol red, PAH) has offered an interesting tool for the study of enzymatic processes concerned with the tubular transfer mechanisms (41). Advantages of this method are: rigid control of the fluid medium, lack of extrarenal factors, and testing of amounts not tolerated by the animal as a whole. Taggart & Forster (42) found that certain dinitrophenols were able to reversibly inhibit phenol red accumulation in flounder tubular cells with no depressing action on cellular respiration; in fact, oxygen consumption was increased. The same type of inhibition of phenol red by dinitrophenol was demonstrated by Beyer (43) in guinea pig kidney slices, and by Cross & Taggart for PAH in rabbit kidney slices (44). It probably acts by interrupting phosphorylation reactions. Carinamide has no effect on respiration, but selectively blocks tubular transfer (43). Shideman (48) suggests that it is a succinic dehydrogenase inhibitor. A number of substances including cyanides, mercury, phloridzin, arsenite, fluoride, and others block the transfer systems simultaneously with depression of oxygen consumption, indicating inhibition of enzyme systems concerned with aerobic phases of the energy cycle. On the other hand, when certain substances are added to the substrate (acetate, lactate, and pyruvate), the accumulation of PAH in slices may be greatly accelerated (44).

Pilot experiments of this type on kidney slices have pointed the way to application of these principles to *in vivo* experimentation. Thus, 2,4-dinitrophenol was found by Mudge & Taggart (45) to have a significant depressing effect on Tm_{PAH} and secretion of phenol red and diodrast in dogs without alteration of filtration rate or blood flow. Reabsorptive processes of glucose, glycine, sodium, potassium, or phosphate were not affected. Succinate and fumarate also had an inhibitory effect on Tm_{PAH} . Sodium lactate and particularly sodium acetate caused increases in Tm_{PAH} . It was concluded that acetate is an active participant in the PAH transfer mechanism (46). Nicholson (47) found that cyanide depressed glucose reabsorption, phenol red secretion, and ammonia production, while filtration rate remained unchanged. Urea excretion, however, was decreased due to increased back diffusion.

Dehydroacetic acid (DHA), pharmacologically important as an antimicrobial agent, is filtered and reabsorbed, but has a marked depressing action on TmpAH, and on penicillin and phenol red secretion without altering filtration rate or blood flow in dogs (48). It does not affect glucose or phosphate reabsorption, hence is similar to carinimide in its action on the transfer mechanisms. Shideman believes that DHA has an inhibitory effect on the succinic dehydrogenase system, suggesting that such substances as PAH, phenol red, and penicillin derive energy from oxidations proceeding through succinic acid and hence via the Krebs cycle.

THE RENAL CIRCULATION

Alteration of blood flow by experimental modification of hemodynamic factors.—When arterial perfusion pressure to the intact dog kidney was reduced by compression of the aorta just above the renal artery, Selkurt, Hall & Spencer (49) found that creatinine and PAH clearances were well maintained until mean arterial pressure was decreased below about 90 mm. Hg. This evidence of circulatory autonomy was ascribed to afferent arteriolar dilatation. Pitts & Duggan (50) found essentially the same response of the renal circulation to reduction in arterial pressure. With graded constriction of the pulmonary artery in anesthetized dogs, renal blood flow was shown by Berne & Levy to decrease less than cardiac output. This was accompanied by efferent arteriolar constriction, but was offset by afferent arteriolar dilatation, so that the renal fraction was elevated (51).

Experimental elevation of renal venous pressure in dogs to about 30 cm. water resulted in a 15 per cent reduction in direct blood flow, PAH, and creatinine clearance, with no change in the filtration fraction (52). Blake *et al.* (53) in similar experiments did not obtain reduction in clearance until the pressure was increased to 55 cm. water. Calculations applied by Maxwell *et al.* (54), to renal blood flow in human subjects indicate that when venous pressure is elevated from 11 mm. to 22 mm. Hg, a 14 per cent reduction in flow results, in conformity with the observations of Selkurt *et al.* The reason for the kidney's ability to maintain flow in the face of loss of arterial pressure, but not with venous obstruction, is not definitely known, but it seems to be related to the regulatory response of the afferent arterioles to changes in arterial pressure [see also (55)].

Effect of albumin administration and blood transfusion.—Studies have been made during daily administration of salt-poor albumin or intravenous infusion of albumin or plasma (56 to 59). General responses include: increase in blood volume and extracellular fluid volume, increase in arterial and venous pressure, and decreased hematocrit. Renal hemodynamic changes show a large increase in plasma flow, but with inconsistent changes in filtration rate, which may either increase or remain unchanged. Since the most marked change is in plasma flow, filtration fraction invariably decreases. The increase in plasma flow is thought to be the result of renal vasodilatation, probably of the efferent arterioles, secondary to increased blood volume, and is contributed to by decreased viscosity of the blood.

When cross-matched blood is transfused into dogs, polycythemia results with presumable increase in blood viscosity (60). Renal plasma flow (PAH clearance) decreases, although total renal blood flow is unchanged or increases. Filtration rate tends to remain constant so that filtration fraction increases. The increase in filtration fraction is believed to be the result of compensatory afferent arteriolar dilatation, but increased resistance to flow of the more viscous blood in the efferent arterioles may be contributory (195).

Response of blood flow to drugs and anesthesia.—A phthalazine derivative (5968 Ciba) has been found to produce renal hyperemia in man (61). Other drugs which have been investigated have a constrictor action: tetraethylammonium bromide (62), DHO-180 (63), histamine (64), neosynephrine (65), and morphine (66).

Anesthesia modifies renal circulation and function in three general ways: Alteration of hormonal or humoral factors which in turn modify renal function, direct or reflex vasomotor changes, or by tubular damage (67). Prolonged light surgical anesthesia with pentobarbital in dogs tends to decrease the PAH clearance, while filtration rate tends to be maintained (68). Filtration rate appears to be a function of the depth of anesthesia in studies conducted with pentothal (69), for the lowest values were obtained with deepest anesthesia. When diffusion respiration was studied in dogs with respiratory arrest (pentothal), profound anuria was noted (70). The effect was much less when the renal nerves were blocked with local anesthesia, suggesting a reflex vasomotor basis for the anuria, probably the result of the associated hypercapnia. Temporary renal denervation during extradural metycaïne anesthesia in man (6T-3L) caused a small drop in arterial pressure, but filtration and plasma flow (PAH clearance) were maintained so that calculated renal resistance decreased (71).

The Trueta mechanism.—Although this mechanism has been extensively reviewed in the previous edition of this series, the impact made by this hypothesis has created reverberations which still echo in investigative circles. The relevant data covered by the period of the present review permit certain conclusions as to whether or not such a functional shunting of blood from the cortex through medullary vascular channels occurs during various experimental procedures.

Franklin *et al.* (72) describe "anoxic diversion of the renal cortical blood flow" in rabbits and other animals during the course of tracheal occlusion and carbon monoxide poisoning. This is manifested by pallor and shrinking of the organ with anemia of the cortex in section, and was prevented by denervation. Arcadi & Farman (73) believed that they had demonstrated two circulations by India ink injection techniques in rabbits following pilocarpine and magnesium sulfate injections which gave cortical hyperemia, or after dehydration by catharsis, which resulted in cortical ischemia. Anesthetized rabbits and rats were scalded by dipping in hot water and the influence on renal circulation was studied by India ink and Prussian

blue distribution (74). Generally, exclusion of circulation from the cortex was demonstrated. Goodwin, Sloan & Scott (75), by means of dye and ink injection and thorotrast radiographic visualization, studied the effects of limb tourniquet and nerve stimulation in rabbits and dogs. Greatest success was obtained by direct renal nerve stimulation, which produced unilateral cortical ischemia, but they confess uncertainty that this represents a "shunt" for increase of blood flow through the medulla was not proved. Kahn *et al.* (76) studied ink distribution in rabbit kidneys under a wide variety of conditions and found no evidence resembling the Trueta effect except in three rabbits where the cortex was free of ink during sciatic stimulation. Moyer *et al.* (77) found ink equally distributed throughout all glomeruli of rabbit and dog kidneys during sciatic stimulation, but with epinephrine injections evidences of cortical ischemia were found.

In summarizing the above studies, it is clear that regional cortical ischemia can be demonstrated under a variety of conditions employing visualization techniques, but in no instance is there unequivocal demonstration of increased shunting of blood through juxta-medullary channels. We may now direct our attention to studies which have attempted to evaluate the hypothesis by means of techniques which measure renal blood flow.

Epinephrine injection and shock in rabbits produced marked reduction in extraction ratio of PAH so that negative values were the rule, accompanied by radiographic evidence of juxtamedullary shunting (78). Dissociation of clearances from direct blood flow, with low extraction ratios of PAH results from operative trauma in cats (79). These workers concluded that a medullary shunt existed, but that it was largely nonglomerular [see also Barrie *et al.* (80)]. But care must be taken that such conclusions are warranted when gross reduction of renal blood flow produces tubular impairment and low extraction ratios of PAH. Thus, although clearance and direct blood flow measurements agree well under normal conditions, after prolonged ischemia marked disparities occur. That these result from tubular damage is evidenced by the fact that when the Fick principle is employed, the blood flow so determined again agrees with direct blood flow (81).

Species difference, or possibly difference in technique, may explain the variance of response seen in the dog (82). Here, epinephrine caused marked decrease in filtration rate, blood flow, and urine volume, but extractions of PAH, creatinine, and oxygen were not significantly decreased, nor was T_{MG} or T_{MPAH} reduced. Therefore, no appreciable shunting of blood from the cortex to the medulla was indicated. Reubi & Schroeder (83) observed little or no change in extraction of PAH and mannitol after epinephrine and histamine in dog and man and thus found little evidence of the Trueta hypothesis operating under these conditions. Nor could evidence be adduced from changes in oxygen content of the renal vein blood, for the A-V difference increases instead of decreasing as it should to fit the hypothesis (77, 83). Increase in the A-V difference is to be expected if the kidneys use a constant amount of oxygen in the face of reduced renal blood flow.

In summary, the results of blood flow studies in dog and man fail to support the Trueta hypothesis and seem inconclusive in the rabbit and cat. However, before final conclusions can be made, further work comparing direct renal blood flow and clearances is indicated with meticulous attention to details such as emptying delay and assurance of normal tubular function under the conditions of the experiment. It would seem advisable, when describing experimental or pathological alteration of the renal circulation, to distinguish clearly between cortical ischemia and true diversion of the cortical blood flow through the juxtamedullary circulation.

ELECTROLYTE CLEARANCE

Sodium.—The hypothesis of Wesson, Anslow & Smith (84) postulates that about 85 per cent of filtered sodium and water is reabsorbed in the proximal tubule and loop of Henle by processes which maintain isosmotic equilibrium, with further reabsorption of salt and water in the distal convoluted by independent processes. Water follows by passive diffusion the active process in the distal segment, governed by secretion of antidiuretic hormone (ADH), so that under given conditions a $Tm^d_{H_2O}$ exists. Also, under conditions conducive to stability, the distal reabsorption of sodium is limited (Tm^d_{Na}). Thus, tubular reabsorption of sodium should depend both on filtration rate and plasma sodium level. This concept has received support from the work of Mudge *et al.* (85).

Experimental work in animals tends to support the hypothesis that a Tm_{Na} may exist. When glomerular filtration rate is rapidly decreased, sodium excretion diminishes to the vanishing point (49, 50, 86) and low filtration rate relative to tubular reabsorptive capacity may account for the poor diuretic response to hypertonic saline in infants (87). Conversely, when sodium chloride load is enhanced in dogs both by increase in filtration rate and elevation of plasma concentration, marked urinary excretion follows (88, 89, 90) and total reabsorption appears to reach a limiting value (91). Acceptance of such a concept should await the accumulation of further knowledge of the influence of associated anions on the tubular responsiveness to sodium, for it has been demonstrated that sodium sulfate (92) and citrate (93) are handled differently from sodium chloride. The exact mechanism of limitation of sodium reabsorption is not apparent, but it is certainly concerned with the balance of hormones secreted by the adrenal cortex and the neurohypophysis. Indeed, Green (90) postulates that the tubular rejection of sodium during hypertonic loading results from increased osmotic pressure of the extracellular fluid relative to the intracellular fluid, a view taken by Seldin & Tarail (94). This is no doubt mediated by osmoreceptors in or near the neurohypophysis and, in turn, the output of ADH. The natriuretic action of ADH has again been confirmed (95).

Present evidence indicates that regulation by the adrenal cortex is not sensitive to rapid fluctuations in osmotic pressure (96), and hence plays

no role in acute experiments involving rapid loading. The adrenal cortex plays a more important role in gradual alteration in tubular kinetics, such as occur during the course of low sodium diet (97), when reabsorptive efficiency increases due to a greater output of desoxycorticosterone-like hormones (98). Daughaday & MacBryde (99), however, dispute the latter claim with the finding of constant output of "corticoids" and 17-ketosteroids during salt deprivation, although their methods are admittedly not specific for the "salt-retaining" hormone.

Potassium.—Further evidence of a dual tubular mechanism for this ion has accumulated, largely from the experimental work of Mudge, Foulks & Gilman (100, 101, 102). Maximal tubular secretion in dogs results from pretreatment with potassium chloride, and minimal secretion during water diuresis. In the latter circumstance, the predominant mechanisms operative are filtration and reabsorption. Increase in intracellular potassium is believed to be basic for stimulation of the secretory mechanism. When conditions for maximal secretion are established, carinamide, phloridzin, dinitrophenol, cinchoninic acid, tetrathionate, PAH, and diodrast do not block secretion. Desoxycorticosterone acetate (DOCA) and adrenocorticotrophic hormone (ACTH) block reabsorption, but apparently do not influence secretion. The mercurials, however, block both reabsorption and secretion, reversed by British Anti-Lewisite. Lithium, itself filtered and reabsorbed, in combination with osmotic diuresis promotes secretion of potassium. The opinion is ventured that the major portion of the filtered potassium is destined for reabsorption, and that potassium found in the urine is secreted. Leaf & Camara (103) present evidence of tubular secretion of potassium in man with ratios of excreted/filtered of 1.21 to 1.64 in chronic glomerulonephritis and polycystic kidney.

Other electrolytes.—A "threshold" exists at about 25 to 27 mM per l. of plasma bicarbonate in man above which a relatively constant quantity averaging 2.8 mM per 100 ml. of glomerular filtrate is reabsorbed (104). Severe osmotic diuresis in dogs is accompanied by increased chloride excretion (105). Tubular reabsorption of chloride and bicarbonate appears to be reciprocally related to the extent that when decreased bicarbonate load results during ammonium chloride acidosis in man, chloride reabsorption increases with accompanying sodium as a base-conserving mechanism (106). Wolf & Ball have examined calcium excretion in dogs and conclude that there is no effective "threshold of retention" and that plasma concentration of this ion is not extensively regulated by renal function (107). Barclay *et al.* (108) consider the possibility of tubular secretion of phosphate to explain the observed decrease in phosphate/filtration rate ratio as plasma phosphorus exceeds 18 mg. per cent. The fact that PAH clearance is depressed at elevated phosphate levels lends support to the idea, but the possibility of toxic action of phosphorus on tubular cells cannot be excluded.

WATER EXCRETION

Regulation of urine flow.—The dominant role of ADH in regulation of urine volume is generally accepted, but details of regulation of its secretion, the role of other humoral factors, and the effects of renal hemodynamics on urine volume continue to be investigated. Pain resulting from muscle ischemia causes inhibition of water diuresis accompanied by chloruresis, implying increased output of ADH on a reflex basis (109). The complexity of reflex regulation is illustrated by the fact that cold causes a diuresis with decreased chloride content, suggesting inhibition of ADH output, for renal clearances are not significantly altered (110). Increased ADH in urine of man results from dehydration, fainting, and electroconvulsive therapy, but not after "blackout" from acceleration; none was found in urine of eclampsics (111). Faradic stimuli applied to rabbits causes oliguria by renal vasoconstriction which persists in the denervated kidney, suggesting a humoral basis. The suggested agent is sympathin (112). Localized stimulation of the hypothalamus in cats results in a decrease in urine flow presumably independent of general arterial pressure effects or posterior pituitary lobe stimulation (113). The view is favored that some specific efferent nervous pathway regulates glomerular filtration.

Other factors which govern the volume of urine are the rate of destruction of ADH and change in tubular reactivity to the hormone. Inactivation apparently occurs in the liver (114), so that with liver damage water retention occurs and edema is favored, as in cirrhosis (115). An ADH-like factor has been found in the urine during nutritional edema (116), its presence favored by subclinical liver impairment resulting from starvation and protein depletion. According to Dicker (117), the reduction of urine volume occurring during protein-deficient diet in rats results from increase in the effective ADH level in early phases, followed by decrease in filtration rate and sodium retention in later phases. In interpreting possible ADH mechanisms, it should be pointed out that substances other than posterior lobe secretions have antidiuretic activity, such as ferritin and apoferritin (118). Heller & Zaimis (119) postulate a low reactivity to ADH of the infant kidney tubules to account for its low concentrating ability. The lower urine volume with increased concentration elaborated at night by the human kidney may be due to increased elaboration, or alternatively, better tubular utilization of existing levels of ADH (120).

Gaunt, Birnie & Eversole have marshalled numerous facts to establish the hypothesis that the renal excretion of water is regulated by a dual, antagonistic control (121). The well-known antidiuretic, chloruretic action of the hormone of the neurohypophysis is opposed by a diuretic, electrolyte-retaining action of the adrenal cortical hormones attributed to: (a) maintenance of filtration and plasma flow, (b) direct inhibition of tubular reabsorption of water, and (c) interference with formation or accumulation of ADH. This is harmonized with the sodium-retaining action of cortical substances when it occurs, by the fact that this leads to thirst and expansion of the

extracellular volume and, eventually, acting together with other factors augments water exchange.

The relation of urine volume to filtration rate has always been a problem of interest, stemming from the obvious control exerted by glomerular intermittency in amphibia. Evidence of opening and closing of nephron circuits in the dog kidney has been advanced by Handley *et al.* under conditions of extreme hydration and dehydration (122) and with morphine action (66). This is based on the finding of proportional changes in filtration rate, T_{MG} , and T_{MPAH} . The findings of Last *et al.* appear to support this concept (123). In dogs with experimental diabetes insipidus, in which the anterior lobe of the hypophysis is believed to be intact, proportional reduction in filtration rate, T_{MG} , and T_{MPAH} occurs, again interpreted to be due to closure of nephron circuits and is considered a mechanism for water conservation (66, 124). The rabbit, formerly thought to regulate urine output by changes in glomerular filtration, has now been shown to be capable of 16-fold change in urine volume without significant change in filtration rate when psychogenic factors are controlled (112). In man, there is no change in plasma flow when urine flow varies from 5 to 20 ml. per min. (125), but mannitol clearance averages only 74 ml. per min. at urine volumes of less than 1 ml. per min. (126). Since T_{MG} was not examined in the last study, this cannot be taken as evidence of glomerular closure in man.

Diuretics.—Because the excellent review of Pitts & Sartorius on the action and uses of diuretics appeared during the period of this review (127), and because of limitations of space, only brief reference to this subject will be given. Besides one study on the mechanism of action of theophylline in normals and congestive heart failure (128), they are concerned with the mercurials. These are devoted to the absorption, distribution, and excretion of mercurials (129, 130), the mechanism and site of action (50, 131), untoward effects and toxic manifestations (132 to 137), and clinical experience, with emphasis on the new preparation, thiomerin (138 to 148).

FACTORS WHICH ALTER RENAL FUNCTION

Age.—The overall relationship of renal function to age shows that it is relatively poor in the infant but reaches adult standards at the age of one or two years. Roughly, from the age of 40 years on, a regression sets in until, at extreme old age, function decreases to about one-half of the normal adult standards. All clearances are corrected to a surface area of 1.73 sq. m. In the infant, filtration rate is only 50 ml. per min., plasma flow 100 to 300 ml. per min., so that the filtration fraction is higher than in the adult (149, 150). T_{MPAH} ranges from 3 to 15 mg. per min. Urea clearance is proportionally low and shows no clear distinction between "standard" and "maximal" rates (151). Comparison of function in normal adults in the age group averaging 20 years with that averaging 90 shows a decrease in function of 46 per cent for C_{IN} , 53 per cent for C_D , and 43.5 per cent for T_{MD} , with a tendency for filtration fraction to increase (26, 152).

Exercise and environmental stress.—Moderate exercise (walking up a grade) caused a 25 per cent (153) and 40 per cent (154) decrease in plasma flow in man, but with no significant change in filtration rate. In hot environments (50°C. dry bulb), resting plasma flow was 39 per cent less than in a cool environment (21°C.), and filtration rate was 21 per cent less (154). With exercise, both functions decreased further, with added increase in filtration fraction. Thus, both heat and exercise produce reduction in renal blood flow by efferent arteriolar constriction. Strenuous exercise causes marked decrease in uric acid clearance (155) which persists for about an hour after exercise, and is in some manner related to increase in lactate production. Decrease in sodium excretion has been noted in dogs exercised on a treadmill, in some cases without alteration in filtration rate, suggesting operation of a hormonal factor (156).

Kenney (157) has studied the effects of four days of water deprivation with adequate diet in three subjects. During this period plasma flow and filtration rate decreased by about a third of control, with slight increase in filtration fraction. Urine was decreased in volume and showed increase in specific gravity and decrease in pH.

Pregnancy.—During the period 11 to 37 weeks of pregnancy, inulin clearances are significantly elevated, averaging 183 ml. per min. per 1.73 sq. m. Beyond 38 weeks, they tend to return to normal values. Urea and PAH followed the inulin in direction but not in magnitude (158). Chesley found significant differences in urea and uric acid clearance during normal pregnancy as compared to preeclampsia (159). In the latter, both clearances are reduced, but uric acid more so than urea. A valuable diagnostic sign for impending eclampsia may be the finding that decrease in uric acid clearance occurs before other symptoms.

Hormones.—White, Heinbecker & Rolf (160, 161) advance evidence to show that the renotrophic effect of the anterior lobe of the hypophysis may be identified with the growth principle. DOCA increases filtration rate and plasma flow in dogs (162) which is related to increase in blood volume and/or extracellular fluid volume, but in some unexplained manner depresses Tm_{PAH} . However, adrenal cortical extracts were found to have no consistent effect on renal function (163) and have no influence on Tm_{PAH} (164). Cortical extracts do not contain significant amounts of DOCA (163), which may account for the difference of response. Desoxycorticosterone glucoside (DCG) causes glycosuria without change in filtration rate as the result of depression of Tm_G (165), but DOCA did not depress Tm_G , indicating a specific property of the glucoside rather than the free steroid. ACTH has been known to cause glycosuria in humans, both as the result of hyperglycemia and possibly depression of the glucose reabsorption mechanism (166, 167). Possibly some cortical hormone similar to DCG mediates the response.

Thyroxine increases filtration rate, plasma flow, and Tm_G in dogs, as does dinitrophenol, suggesting that the response may be a general metabolic one causing activation of more nephron circuits, rather than a specific effect on tubular enzyme systems, according to Handley (168). Testosterone pro-

prionate was found to be without effect on renal function, but estradiol benzoate resulted in decrease of T_{PAH} by nonspecific depression of the enzyme systems (169).

RENAL FUNCTION IN PATHOLOGICAL STATES

Earle (170) has reviewed the principles of application of clearance techniques to the well-known nephropathies. Specific measurements for types of renal damage are: glomerular filtration rate, C_{IN} ; renal plasma flow, C_{PAH} ; proximal tubule: T_{PAH} and T_{MG} ; distal tubule: concentration-dilution, electrolyte balance, acid-base balance, and ammonia formation. Discussion of the following section will usually involve these or similar measurements.

Congestive heart failure.—Heller & Jacobson (171) have classified cardiac disease into three categories for evaluation of renal hemodynamic changes. In patients with a history of rheumatic heart disease, but never in congestive failure, plasma flow (PAH) averaged 72 per cent of their normal series; in congestive failure, but edema free, 53 per cent of normal; and in decompensation with edema, 31.5 per cent of normal. Corresponding changes in filtration rate (mannitol) were respectively 98, 83, and 73 per cent of normal. T_{PAH} in the three groups was 73.1, 71.6, and 44.2 mg. per min., compared to the control average of 80.3. The reduction of T_{PAH} is of particular interest in view of the reported normal extraction of PAH in congestive failure (54). The authors attribute the change to the effects of tubular ischemia in localized areas.

The decrease of plasma flow in the first group, presumably by efferent arteriolar constriction, is noteworthy because it precedes elevation of venous pressure and edema, leading them to conclude that a contributory factor to edema formation is renal ischemia and decrease in sodium load to the tubules with retention, for which there is experimental evidence (49, 50). They also believe that other factors are operative, for remission of edema with clinical improvement is not associated with significant increase in filtration rate. Other workers observed lack of correlation between filtration rate and sodium excretion in congestive failure (128, 172, 173, 173a) and look for factors, probably hormonal, which modify the tubular reactivity to salt and water. Anoxia, a possible complication, apparently causes increased excretion of sodium chloride rather than retention (174). Of considerable interest is the fact that patients with cardiac failure show increased excretion of antidiuretic substances (175, 176) and adrenal corticoids (177), but integration of these observations with the complex physiological disturbances leading to cardiac edema will prove difficult.

Another factor believed by some workers to be important in contributing to edema formation is the elevated venous pressure associated with this condition (54, 171). Experimental elevation of renal venous pressure in dogs is followed by reduction in sodium excretion (53, 178). This type of mechanism is believed by Fishman *et al.* (179) to be the basis for the edema produced by experimental chronic pericarditis in dogs, where sodium excretion diminished coincidentally with increase in venous pressure, and before changes in

cardiac output and renal plasma flow and filtration rate were observed.

Glomerulonephritis.—In confirmation of previous findings, the major alteration is impairment of filtration rate (180, 181, 182). This declines to a greater degree than plasma flow, so the filtration fraction is decreased. But extraction of PAH is impaired, proving coexistence of tubular damage. When this factor is taken into account, total blood flow may be in the upper range of normal, suggesting a relative hyperemia. In severe cases, blood flow is reduced due to glomerular capillary obstruction and increased intrarenal pressure. The glomerulo-tubular imbalance favors better reabsorption of reduced loads of sodium and water, a contributory factor to the edema which is frequently associated.

Hypertension.—Extraction of PAH is normal in essential hypertension, so that the observed increase in filtration fraction is unquestionably due to efferent arteriolar constriction. More severe tubular damage supervenes with nephrosclerotic changes, as shown by reduced PAH extraction (range, 64 to 80 per cent) (181). In dogs with hypertension, spontaneous (essential?) or produced with a Goldblatt clamp, no progressive alteration in renal clearances was noted for periods of observation extending up to 120 weeks (183). Abscess formation resulting from injection of CCl_4 or turpentine exerted a depressor action on hypertension of both types, with increase in renal plasma flow but constant filtration rate. This reversible response of the renal circulation suggests a dynamic vasoconstriction rather than an anatomically fixed vascular modification (184). When hypertensin is injected into rabbits, it causes no significant change in inulin clearance, but diodrast clearance is decreased, so that the filtration fraction increases, in keeping with the change noted in essential hypertension (185).

Acute nephrosis.—The oliguria and markedly reduced clearances resulting from carbon tetrachloride poisoning in man are primarily due to tubular damage and back diffusion, according to Sirota (186), but an early phase of reduced blood flow (determined by the Fick method) may result from interstitial edema and inflammatory swelling. Final repair takes 100 to 200 days, with Tm_{PAH} showing the greatest rate of recovery. Two hours of complete renal ischemia in dogs causes severe reduction in clearances, but direct plasma flow (Fick method) may not be altered, suggesting that back-diffusion here again may be the cause of the reduced clearances (187), a view favored by Földi (188). Bacitracin results in reduction of inulin and PAH clearance, and Tm_{PAH} and Tm_{G} to about two-thirds of normal in humans, with recovery taking 6 to 9 weeks (189). During the alkalosis and dehydration resulting from vomiting of pyloric stenosis, severely diminished inulin and PAH clearances and Tm_{PAH} occur due to tubular impairment (190).

Uretral obstruction.—Blocking the ureter for about an hour in dogs causes a temporary increase in urine flow, despite decrease in filtration rate, indicating impaired active water reabsorption (191). No significant effect on plasma flow or electrolyte clearance occurred. Effects are undoubtedly more severe with longer periods of partial or complete uretral blockage. Evidence

of reduced blood flow was demonstrated in rabbits by thorotrast and cine-radiography 24 hr. after unilateral division of the ureter (192). A patient with partial unilateral uretral stricture exhibited diminished excretion of phenol red, uric acid, and phosphate, but not of calcium compared to the normal kidney. This was restored by repair of the stricture (193). Histological evidence of impaired blood flow is observed following prolonged obstruction (211, 212).

Miscellaneous.—Thiosulfate clearance is reduced in children with sickle cell anemia (194). In congenital cyanotic heart disease with polycythemia (195), inulin clearances are normal, but plasma flow (PAH) is about half of normal, so that filtration fraction is increased to 0.31. Total blood flow is actually about 40 per cent above normal so that the renal fraction of the cardiac output averages 35 per cent compared to the normal figure of 21.5 per cent. The increase in filtration fraction is thought to be due to increased viscosity of blood acting in the efferent arterioles. [Compare to experimental polycythemia (60).] Marked variation in C_{IN} , C_{PAH} , and Tm_{PAH} has been observed in multiple myeloma, but since Tm_{PAH} is least impaired, the suggestion is made that vascular changes are more prominent than tubular damage (196). Paraplegics show impaired phenol-red excretion, but some of these exhibit normal dilution-concentration tests, suggesting that tubular secretion is impaired before reabsorption (197).

RENAL PATHOLOGY

Shock kidney.—Burch & Ray (198) review the clinical picture, etiology, pathology, and treatment of "lower nephron" syndrome. It has been generally accepted that glomerular and proximal tubular damage are minimal, and that major damage exists in the distal convoluted tubule. Oliver looks on the distal segment as the point of special pathogenic importance because urinary concentration and decrease in pH occurs here (199). However, impaired glomerular filtration may contribute to the "toxic oliguria," and ample evidence of proximal tubular damage exists. Thus, French (200) in examination of kidneys from patients succumbing to conditions of varied etiology but acceptable as causing "lower nephron" syndrome found swelling of the glomerular epithelium and thickening of capillary walls, and manifestations of damage in the proximal tubules (cloudy swelling, hydropic changes, and simple necrosis). He accordingly employs the more general term "glomerulonephrosis" to describe the condition. This designation may aptly be applied to other nephropathies which manifest glomerular and proximal tubular changes, as well as distal tubular changes, e.g., those in association with chronic ulcerative colitis (201, 202), in symmetrical cortical necrosis of infancy and children (203), and septic abortion kidney (204, 205). These conditions exhibit a complex background of dehydration and electrolyte disturbance, sepsis, and in septic abortion, toxic materials from degenerating placental tissue. Liver impairment is a frequent accompaniment, giving rise to the term "hepato-renal syndrome."

Nephritis and nephrosis.—Extensive reviews on the nephrotic syndrome have appeared (206, 207). Barnes *et al.* (207) set up criteria for distinguishing between lipoid nephrosis and the nephrotic stage of chronic glomerulonephritis. Vancura reviews the pathogenesis of acute glomerulonephritis and divides it into early and late phases (208). The early phase of simple albuminuria is considered to be the result of bacterial toxins, and the late phase, marked by oliguria, edema, hypertension, and diffuse glomerular lesions is compared to Masugi's nephritis following changes in immunobiological reaction.

Pyelonephritis and polycystic kidney.—Birchall & Alexander (209), in an excellent review of pyelonephritis, outline a systematic approach to the problem of treatment with emphasis on eradication of the disease rather than simply making the urine sterile. The causal relationship of pyelonephritis to renal papillary necrosis is emphasized, particularly in diabetics (210, 211, 212). Rall & Odel (213) review 207 cases of polycystic kidney disease and emphasize the high related incidence of hypertensive changes.

Experimental nephropathies.—The glomeruli are the source of the antigen that produces nephrotoxic antiserum which, when reinjected into test animals, produces albuminuria and glomerulo-nephritis (214, 215, 216). Investigations of the role of hemoglobin in the production of nephrosis of the type associated with "lower nephron" syndrome indicate that the state of hydration of the animal and the absolute level of hemoglobinemia are important factors in the outcome (217, 218, 219). Tubular lesions have been produced by combined ligation of the bile duct and renal ischemia (bile nephrosis) (220, 221), pteroylglutamic acid (222), choline deficiency (223), pectin (224), India ink and carmine injection (225), hypopotassemia (226), dehydration (227), and hyperglobulinemia (228). With hyperglobulinemia, glomerular lesions resembling those of glomerulosclerosis are produced. Attempts to reproduce papillary necrosis by ligation of the ureters result in pyelonephritis and hydronephrosis followed by necrosis of the renal papillae in dogs (211), but not in rats (212). Studies of renal hypertrophy after unilateral nephrectomy in rats prove that the increase in size is due both to hypertrophy of cells and hyperplasia (229, 230) with greatest mitotic activity two days after nephrectomy. Some ability to hypertrophy remains after complete ischemia lasting up to three hours (231). Functional studies in dogs correlate well with the above morphological findings, with compensatory increase in filtration rate, plasma flow, and Tm_{PAH} evident in two days (232).

TREATMENT OF ACUTE RENAL FAILURE

The treatment of acute renal failure, whatever its origin, falls into two general categories: (a) management by conservative therapy with careful attention to diet and electrolyte balance, and (b) the use of artificial dialyzing devices.

Conservative therapy emphasizes the fact that if a patient survives about

12 days of anuria or oliguria, the chances of eventual recovery are good. He is aided through this period by strict attention to fluid and electrolyte intake in diet which should match the amount lost by metabolic processes or by vomit and diarrhea. Fasting and protein in the diet are deleterious (233, 234), and fats and carbohydrate are recommended, the latter by intravenous infusion if necessary as 5 per cent glucose. Details of management and the extent of success of conservative management appear in a number of reports (235 to 242). It is well to emphasize that those advocating the use of dialysis methods should keep in mind the possibility of spontaneous recovery in evaluating the efficacy of their methods.

Artificial kidney.—Details which have been troublesome in previous clinical application appear to have been surmounted in the meticulous application of a modified Kolff device by Merrill *et al.* (243, 244). Its application 60 times in 43 patients gives support to the claim that repeated use can be accomplished without hazard to the patient and should not be postponed as a last resort. In their hands, urea was removed at the rate of 10 to 12 gm. per hr., but it was used for relief of conditions varying as widely as pulmonary edema and barbiturate intoxication. The conclusion of Fishman *et al.* (245), after clinical trial of the Kolff kidney, showed that it is mechanically capable of efficient and rapid dialysis. For success, irreversible changes must not be permitted before dialysis is undertaken. Murray, Delorme & Thomas (246) claim about 50 per cent survival of patients treated with their model. Vanatta, Muirhead & Grollman (247) have improved survival time in dogs by strict attention to technical details, especially composition of the dialysate fluid. Skeggs, Leonards & Heisler (248) present preliminary results of application of their revolutionary model to dogs. Urea clearance is 50 ml. per min.

Peritoneal lavage.—Fenn *et al.* (249) state frankly after their experience with this method: "The maintenance of proper electrolyte balance of the extracellular fluid will probably be the key to success in most cases treated by this method." Edema and convulsions are the outcome of poor electrolyte management (250). The use of antibiotics seems to have been successful in warding off proneness to bacterial invasion. The method has been tried with significant reduction of blood urea nitrogen in children (251), including an infant of 8 months (252), but it is doubtful if in these cases that survival time was prolonged. An attempt has been made to relieve intractable cardiac edema (253).

Intestinal perfusion and other methods.—This method has the advantage of not requiring aseptic technique, but is undoubtedly unpleasant to the patient, and the risk of electrolyte disturbance is present as with the other dialysis techniques (254, 255, 256). The method seems particularly prone to cause potassium depletion, possibly because of its secretion in the intestinal juices. Other methods which have been tried include experimental cross-transfusion in dogs to relieve effects of acute mercury nephroses (257), and replacement transfusions (258). Although the latter method minimizes

electrolyte and acid base balance disturbances, tremendous amounts of donor blood are used (as much as 41 l. in one case!), presenting imminent danger of improperly matched blood.

METHODS

Improvements in the diphenylamine method for inulin determination have been suggested (259, 260). A simplified resorcinol method which avoids yeasting has been recommended by two laboratories (261, 262). Increasing use of the clearance of endogenous creatinine for the measurement of glomerular filtration has led to the development of an analytical method for use on small quantities of serum and urine, employing the principle of elution with Lloyd's reagent (263). A more sensitive method for analysis of ferrocyanide will permit use of lower blood levels, thus avoiding toxic reactions (264). A convenient method for determination of urea in blood and urine has been described (265). An improved uric acid method is presented (266). Construction and use of flame photometers is the subject of three reports (267, 268, 269). A rapid, simple method for continuous estimation of serum total base based on the electrical conductivity method may prove useful in conjunction with the artificial kidney or peritoneal lavage (270). Munnell & Gregg (271) have devised a clamp ($1.7 \times 1.65 \times 1.5$ mm.!) for production of renal hypertension in rats. In keeping with the times, renal hypertension may now be produced with a plastic capsule (272). An ingenious method of estimating renal blood flow with a two-channel photofluorometer sensitive to fluorescein has been described (273). Direct renal blood flow is measured by an optically recording bubble flowmeter (274).

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CONDUCTION AND TRANSMISSION OF NERVE IMPULSES

BY THEODORE HOLMES BULLOCK

Department of Zoology, University of California, Los Angeles, California

The last year or two has seen some of the most striking and significant advances in many years in our knowledge of mechanisms at the unit level. Resolution of the long-standing inadequacy of the Bernstein theory to account for overshoot of the action potential (6) seems at hand and the new concept is already repeatedly confirmed (9, 10, 12, 14, 126). Zero-net-membrane-current action potentials have been recorded across the membrane (21). Space distribution of excitation around stimulating electrodes and the long-disputed distortions by connective tissue sheaths have been all but definitively analyzed (29 to 33). Saltatory conduction in nodal fibers is directly demonstrated after years of doubts and denials (64). New tools of great power for refined electrical measurement of passive and active membrane properties, useable in whole nerves, have been developed (53). The discovery of new junctions has extended the range of properties of transmission, if not of its mechanism, giving promise of a real systemization with some perspective on common and derived properties (46, 84, 85, 86, 89, 106, 145).

This review will develop only certain themes, especially some which are of controversial status, paying the price of omission of some worthy papers and of uneasy partisanship with its false appearance of unappreciative estimation of others. It draws chiefly on the literature from June 1949 to June 1950. Other recent reviews covering this ground include those by Grundfest (1), van Harreveld (2), Blair (3), Katz (4) and Lloyd & McIntyre (5).

MECHANISM OF ELECTRIC POTENTIALS

Hodgkin & Katz (6) have brought experiment to bear upon the long known fact that the nerve fiber membrane not only maintains a steep gradient of potassium concentration, with the high inside, but one of sodium concentration, with the low inside in the resting state. They construct an hypothesis upon this fact by assuming that at rest the membrane is much more permeable to potassium than to sodium and in action much more permeable to sodium than to potassium. The consequence of this, when the external sodium is much higher than the internal, will be an action potential which exceeds the resting potential, reversing the polarity of the membrane. The latter, of course, is the observed fact, hitherto not explained, which constitutes the chief discrepancy between classical membrane theory and experience. The beauty of the present proposal is its amenability to experimental test. By assuming that the active state results from a great increase in the sodium permeability (P_{Na}) without change in P_K , it will be expected that the resting membrane potential is chiefly affected by external potassium [in

agreement with Shanes (7)], and approaches a potassium electrode, while the action potential should be chiefly a function of external sodium, approaching a sodium electrode. They find that small deficits or increases in external sodium produce a small effect on resting potential, a large effect on action potential, the slope of which agrees with the theoretical 58 mv. per tenfold concentration change.¹ The action potential is reversibly abolished by sodium-free medium and is reduced to a value equal to the resting potential, i.e., the overshoot is zero at about 30 per cent normal outside sodium. As predicted, there is a simultaneous effect on rate of rise of action potential and speed of conduction. All the effects are specific to sodium.

Anticipating objections to the hypothesis, the authors admit it is

difficult to accept the assumption that the active membrane can become selectively permeable to sodium. We therefore suggest that sodium does not cross the membrane in ionic form, but enters into combination with a lipid soluble carrier in the membrane which is only free to move when the membrane is depolarized.

Actually, it would seem that it must begin transporting sodium before the action potential has reached this halfway point. In any case, such a suggestion offers a real opportunity to look for the specific role which it seems very likely acetylcholine plays in the action potential mechanism (see p. 273).

On certain assumptions an equation for the relation between potential and potassium, sodium, and chloride activities (roughly concentration) inside and outside and the membrane permeabilities to these constituents is derived. Although certainly oversimplified, it predicts rather well a large number of effects with various solutions when $P_K:P_{Na}:P_{Cl}$ are taken as 1:0.04:0.45 at rest, 1:20:0.45 in activity and 1.8:0:0.45 at the time of the positive after potential. Deviations are in the direction of less than full sodium permeability under certain conditions. Further tests of these permeability ratios include: (a) The calculated flow rates which they predict for the resting loss of potassium and gain of sodium. These agree with earlier measurements by Steinbach & Spiegelman (149). (b) At the maximum rate of rise of potential the calculated inward flow of current is 1.2 ma. per sq. cm. compared to the observed 0.9 ma. per sq. cm. (c) Assuming the rising phase of action potential is due to sodium entry² and does not overlap with the falling phase of potassium exit, 1.5×10^{-12} mole Na per sq. cm. per impulse should enter as a minimum and the same amount of potassium should leave if $P_K > P_{Cl}$. The agreement is striking between the calculated value for squid fibers and the measurements, by different methods of 1.7×10^{-12}

¹ Lorente de N6 (150), in his latest paper, denies this for frog nerve on the basis that conduction continues after the external sodium is claimed to be almost completely removed, but the contrary findings with single fibers (see footnote 4) appear to be more cogent.

² Recently, Hodgkin & Huxley (151) reported results strongly indicating that sodium entry coincides with the early and potassium exit with the late phase of the action potential.

mole potassium escaping per sq. cm. per impulse (8), and 2.1×10^{-12} (9), both in crab fiber, and 4.5×10^{-12} mole sodium entering per sq. cm. per impulse (10, 11) in squid giant axon.³

Confirmation, by direct measurement, of increased net sodium entry in activity is at hand (10, 11, 12), including demonstration of higher sodium entry with higher frequency of stimulation (126). It is significant for the proposed role of acetylcholine (see below) that permeability to sodium and potassium are markedly increased by anticholinesterases.

Direct confirmation of the membrane reversal during action has been provided by transmembrane measurements in striated muscle (13, 14), in the end plate of the neuromuscular junction (15), in vertebrate nerve, and in heart muscle (16).⁴ Similarly, confirmation of the sodium effect on action potential in muscle is available (14) and follows closely the theoretical slope. Fair agreement with the Nernst relation is obtained for transmembrane resting potential and potassium (17). By way of anticipating the benefits of comparative physiology, it may be expected that interesting tests of the new concept will come from further study of those remarkable insects shown to have high potassium and low sodium in body fluids [Tobias (18, 19)].

The temperature coefficient of the resting potential and of resting potassium and sodium exchange is low, whereas various phases of the action potential have high Q_{10} 's. This is taken to mean that the former is essentially the result of a Donnan equilibrium. The latter depends on limiting rates of chemical events [Rothenberg (12), Nastuk & Hodgkin (14), Hodgkin & Katz (20)].

The first of a series of papers by Marmont extending the transmembrane recording techniques of Curtis, Cole, Hodgkin & Huxley on squid giant axons has appeared (21). It is mainly devoted to a description of an extremely sophisticated technique which permits stimulation, recording, and application of counter potentials controlled by the nerve impulse through one internal and three external electrodes. The latter assure a large area of axon surface at the same potential and therefore exact measurement, for example, of the net number of ions per unit area crossing the membrane during an impulse. One typical result of great interest is presented but not fully discussed—records of normal action potentials under conditions which prevent any net membrane current. Schoepfle & Erlanger (22) show that all suscepti-

³ Keynes & Lewis (152) have now measured sodium and potassium exchange in the same fiber with the aid of a new technique of activation analysis, and they give values among others (all mols $\times 10^{-12}$ per sq. cm. per impulse) of 3.8 for net sodium entry and 3.2 for net potassium loss. There is an outward movement of sodium of about 5 while the inward is about 10 in these units, and an inward movement of potassium of about 0.35 coincides with outward movement of 4.7.

⁴ Huxley & Stämpfli (153) have devised a method for single nodal nerve fibers and find values agreeing closely with invertebrate nerve fibers and muscle. They confirm in the frog the expected sodium effects. Coraboeuf & Weidmann (154) find closely similar resting and action potentials in cardiac muscle.

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ble processes concerned with spike height are altered linearly by applied currents; inward currents are more effective than outward; stored nerves depart from these relations.

Shanes (7, 23, 24) has extended his studies of resting and action potentials under the influence of a number of environmental agents and interprets the results as meaning fluctuating potassium release due to interaction between metabolism and permeability, both being labile [see also (25)]. Potassium shifts are also shown in ganglionic transmission: the output of a radiopotassium-loaded ganglion or the uptake of K^{42} from the blood is increased by preganglionic but not by antidromic stimulation (26). Changes in ionic environment (potassium, pH, calcium) influence ganglionic potentials (27). Monnier provides a general review of the role of calcium in nervous tissue, including speculations on its chemistry (28).

EXCITATION AND CONDUCTION

Rushton & Rashbass, in a series of five exemplary papers (29 to 33), have described studies of the spatial distribution of excitability in whole frog nerve (threshold as function of interelectrode distance). Ingenious experiments prove the classical assumption false that excitation arises at the cathode, when anode and cathode are close together. Rather it arises some 3 mm. away. Nor does excitability fall away from the cathode along an exponential curve. These results are incompatible with the usual interpretation of nerve as equivalent to a cable of ohmic conductors. The discrepancy is shown to be due to the epineurium. When this is stripped off, the agreement with cable theory is good. Direct measurement shows that in whole nerve the epineurium is, in fact, responsible for a large potential drop and altered distribution of potential. Lorente de N6's assertion that "the existence of the connective sheath may be ignored in the analysis of potentials recorded from the surface of nerve" (34, p. 13) is, apparently, definitively disproved.⁵ This requires the rejection or reinterpretation of much of this author's work, for example his "longitudinal polarization." The accuracy, scope and quantitative power of the Rushton-Rashbass analysis cannot be adequately described here, but the series will certainly form the basis for any further work on excitation or electrotonic potential distribution.

New data have been offered on thresholds to electric shocks of various rise times and the differential effect of anelectrotonus on rapid and slowly rising stimuli (35). Analysis of threshold electrotonic potentials supports the view "that local attainment of a critical outwardly directed potential difference across the distributed membrane capacity is sufficient for excitation of nerve in absence of accommodation" (36). Monnier & Coppée (37) recognize a "new characteristic of excitable tissue," i.e., *amortissement* (abatement, deadening) which has, in general the properties and time course of

⁵ Lorente de N6 (150) denies this *in extenso* but fails in particular to throw doubt on the Rushton-Rashbass analysis.

reciprocal excitability and rhythmic instability. Strohl (38) and Gerstner (39, 40) have contributed theoretical papers on core conductors and local excitation, respectively. The modifications in response of mammalian nerve under the influence of low and high temperatures and the differential action of cooling and heating on A and C fibers have been analyzed with respect to the effects of cations and other agents (41, 42). Effects of temperature on rheobase, accommodation, minimum quantity of electricity required to excite, time course of subthreshold response, and recovery have been quantitatively measured on single frog fibers [Tasaki (43)]. The same author studied the collision of two impulses in single fibers and attributes the block not to refractoriness but to lack of the normal internal stimulating current; conduction rate is increased as the impulses approach (44).

Rosenbluth and collaborators (45) criticize the usual subdivision of the refractory period into absolute and relative as experimental artifacts without normal physiological reality. They recognize instead a single period, the functional refractory period (f.r.p.), which is that time during which the action potential of a locus is insufficient in amplitude to reach the threshold of the neighboring region of a nerve fiber. One-way conduction in whole nerve, inferred by eliminating alternative explanations of records under certain conditions, is thus explained by assuming that the curves of amplitude and threshold with distance from a depressed locus are tangential at one point. The increase in latency of a response to a test shock, when conditioning shocks precede it by short intervals, is really a constant elapsed time after the conditioning shock and measures the f.r.p. An extra conditioning shock early in the absolute refractory period can facilitate a test shock given during the relatively refractory period, or if late, can diminish it. It seems highly probable that the local response is responsible for these properties and the authors' interpretations are in good agreement with the known facts about critical amplitude of local response for spike initiation. They propose that at the end of the f.r.p., amplitude (volts of action potential) is equal to threshold; since they find at this time that the amplitude is 0.25 to 0.3 normal and the threshold is 1.8 normal, the safety factor is 6 to 8.

Bullock & Turner (46) confirm one-way conduction directly on single fibers, including spontaneous one-way block and one-way initiation from a locus between polarizing electrodes (after an impulse from distant stimulation has passed). The lability of this latter suggests fluctuating play of excitability and local response, as also does the occasional unstable form of a failing spike described as "sputtering decline." What seem to be similar phenomena have been reported for the responses of a single node of Ranvier at the shortest intervals after a conditioning shock, i.e., small, possibly graded potentials of variable size and form (47). The local response is also implicated (46) as the necessary condition to the phenomenon of death and rebirth of an impulse at a block, confirming and reinterpreting Blair & Erlanger's (48) finding which they believed to represent the jumping of a spike across inactive nodes. All these properties are taken to increase the proba-

bility that the mechanism of conduction is essentially the same as that of transmission, i.e., electrical insofar as stimulation from adjacent tissue is concerned, chemical and physical inside each responding unit (49, 50). It is of some interest to find the reality of the local response in vertebrate nerve [shown by Katz (51, 52), but denied by Lorente de N6 (34)] confirmed by an independent method, the "complex attenuation method" for membrane admittance of Schmitt & Stewart (53). Even at small percentages of threshold, evidence is found for an energy contributing process, strongly time dependent and responsive to the "usual nerve reagents."

Reviving an idea several times discarded, it is reported that some nerve fibers consistently show facilitation of conduction rate, an occurrence which poor condition of the preparation apparently does not explain. Correlation with supernormal excitability is good on the average but individual responses are often of normal speed during supernormal excitability or of supernormal speed during the refractory period, so that a simple explanation on the basis of spike threshold alone may be inadequate [Bullock (54)].⁶ Analogy with the well-known facilitation of synaptic delay seems natural and not forced. Taylor (55) has studied the effect of polarization on velocity of conduction and shows that rate is maximum under weak cathodal current, falling away on either side to as slow as one-half normal rate before block. Interestingly, the relief of potassium chloride block by anodal polarization does not produce normal velocity, but that which normal nerve under the same polarization would show. The effect of stretch on velocity has been reexamined in single fibers permitting direct measurement of diameter while conduction rate is being determined (56). In the usual case, rate is perfectly constant while diameter is reversibly reduced 50 per cent; occasionally, increased rate is observed. Such material would seem to offer rewarding opportunity for close analysis by methods measuring impedance and dielectric. Circumferential pressure exerted by air on a short length of nerve *in situ* does not block as rapidly as pressure exerted by mercury (57). It is concluded that anoxia is responsible for the pressure blocks heretofore reported, at least up to 150 mm. Hg. The eminent practicability of recording sharp, undispersed A fiber action potentials through the human skin and the sensitivity to minor clinical damage has been shown (58). Measurements of velocity in the ulnar nerve of human subjects of different ages, by conventional methods, has shown the error of previous belief that velocity increases *pari passu* with growth in length of nerves. Rate is maximum already at the age of three and is not significantly altered till past sixty, when it declines (59).

NODES AND SALTATORY CONDUCTION

One of the most significant advances of the year is the sudden increase in knowledge of the distribution and properties of nodes of Ranvier. Erlanger & Blair (60) in 1934 had proposed, on the basis of quantal defections of single

⁶ A separate excitability representing rate of rise of local response is suggested.

fiber spikes under anelectrotonus, that the segmentation of myelinated axons is manifest in conduction. Tasaki (61) and von Murralt (62) had supported the concept but it has not been generally accepted (63). Today, it is necessary to say that our gross picture of conduction in such fibers has been more radically altered by one saltation than by the progress of several previous decades. Huxley & Stämpfli (64) have obtained elegant direct evidence of the most telling kind that the earlier suggestions were correct. The conduction time of the longitudinal current external to a single fiber is almost constant through the length of an internode and increases stepwise at each node. The amplitude of this current declines steadily through the length of each internode and recovers stepwise at each node. There is appreciable current crossing the sheath in the internode, but it is a minor fraction. This fraction is explicable as passive current on reasonable values of sheath impedance and capacity. On the other hand, the large current crossing at the node has a time course which requires the assumption of an active process. Although the authors do not make it explicit, the possibility of some active component in the internode cannot be excluded, indeed it would seem to bring the calculated values for membrane passive properties in the right direction for better agreement with those known from other animals. This may be important as a possible ground for reconciling the findings, more recently reported (65, 66), that cold or pressure applied to a small portion of an internode can reversibly block. The probability that these agents are increasing external resistance sufficiently to explain the result seems remote and the authors' conclusion inescapable that the internode is not just a conductor but an essential active participant. Huxley & Stämpfli also extend the earlier knowledge that high resistance external to the sheath (sugar solution replacing electrolytes) can block, to show that it suffices for the high resistance to be confined to a portion of one internode (by using short air gaps). Barring certain special explanations, which they discuss, this may be taken as independent evidence that no adequate longitudinal current passes beneath or in the sheath external to the fiber. In a theoretical discussion they show that a reasonable expectation exists that the speed of conduction will vary with node spacing with a very broad maximum, so that if natural selection has achieved optimum conditions, nodes may be found to be spaced independently of the speed of conduction, as between different fibers. This is indeed the conclusion reached in a quantitative anatomical study of the specially favorable nerves of fishes (67) and is provided for in another way in a theoretical treatment by mathematicians (68).

It is very interesting that at the same time as these demonstrations of the functional meaning of nodes we should also witness an abrupt increase in knowledge of their distribution. Again confirming early reports which had not been accepted, new evidence, based on a valuable new technique [intravenous methylene blue for sectioned central nervous tissue (69)], clearly shows that nodes are common in white matter in the brain and cord (70, 71) spaced proportionally to the diameter of the fiber, probably as a

result of growth factors largely independent of functional significance (72).

The evolution of such a mechanism is of great interest. It probably represents the greatest difference yet found between the properties of neural units in vertebrates and invertebrates. Except for a very few uncertain analogues, nodes are lacking in the latter; sheaths, including myelin, must be much more permeable and external high resistance applied locally should not block. It is amusing that, whereas the old idea of an insulating role cannot be applied to the older animal groups who presumably invented myelin, this idea proves to be the principal achievement of the vertebrates although not in the sense it has had, since the all essential local circuits pass through the tissues outside the sheath. Besides invertebrate fibers, there is still presumably a large category of vertebrate fibers which lack nodes, including the so-called unmyelinated fibers (which probably have thin myelin sheaths).

PHYSICAL PROPERTIES

Tobias & Solomon (73, 74) have confirmed and extended early observations of changes in appearance of nerve under polarization. Small currents suffice to increase opacity, shrinkage, light scattering and rigidity at the anode and the opposite at the cathode. Potassium enhances, calcium inhibits this effect; "anodal agglomeration of cellular colloid with dehydration" is suggested. "Water is probably moved electroendosmotically along the axis of the nerve toward the cathodes." The possibility that such changes occur in normal activity of nerve is still open but it is suggested by the reports (75) that a slow delayed change in absorption of ultraviolet light is left in nerve on stimulation and (76) that opacity first increases then decreases after a train of impulses in crab nerve.

A new attack on electrical characteristics of the membrane (77, 78, 79) promises much but no full publication is yet available. The power of the method is indicated by its ability to utilize nerve fibers not isolated from adhering tissue and whole nerves of sufficient homogeneity or sufficiently marked heterogeneity. This will make possible a much broader base in comparative studies since there are for example many giant fibers otherwise favorable but difficult to isolate.

Tasaki & Mizuguchi (80) have measured the impedance change during activity in single nodal fibers. The decrease in impedance exactly coincides in time with the "actual electromotive force" and is proportional to it in magnitude at every moment; it is not as great a change as Cole & Curtis believed from squid measurements; it is entirely assigned to the region of the node. Burr & Mauro (81) report an electrostatic field of hundreds of microvolts measured in the air several millimeters away from a frog sciatic nerve propagating a response; the form of the voltage plotted against time is quite similar to the action potential taken off the surface of the nerve. A curve is given for the fall-off with distance from the nerve, but the authors feel distortion of the field by the probe is so great that comparison with the theoretically expected rate of decline is not meaningful as yet. Fry & Wulff (82) find that ultrasound at intensities available had no effect on peripheral

nerve function but readily depressed or abolished central activity, both spontaneous and reflex. Temperature rise is excluded as the effective agent.

PROPERTIES OF TRANSMISSION

Among the advances in this area certainly the most dramatic come from comparative studies. Invertebrates continue, at an accelerating pace, to yield preparations permitting analyses of units in a way not possible in higher forms. An outstanding example is the series of remarkable synapses of the giant system in the crayfish. Among these Wiersma & Turner (83, 84) have recently exploited the four large, simple synapses arranged linearly on a single emerging motor fiber. In the fresh preparation each presynaptic fiber fires the postfiber in a 1:1 manner, but after some fatigue spatial or temporal summation becomes necessary. Spatial summation does not succeed if the two presynaptic fibers carry impulses simultaneously or within short intervals. This inert period is longer and the duration of the summation period is shorter the farther apart are the two synapses used. A process increasing excitability and spreading from the first of the two synapses excited, declining with distance and time, is inferred. Clearly, the summed postsynaptic spike arises at the second synapse. The rate of spread was estimated at 0.15 m. per sec., but this figure may be low or high if the second synapse is actually reached by the spreading process (possibly a local response) within a critical period following or preceding the second presynaptic spike. Repetitive excitation of a more peripheral synapse usually blocks a more central one and can maintain a depression even if the former is already blocked. The peripheral junction can block the central before it is itself blocked, indeed sometimes before the central would have been fatigued through its own presynaptic fiber.

The authors are cautious in interpretation but the data are certainly a challenge to the concept of local response. To the reviewer, the facts seem not only compatible with explanation in terms of local response refractoriness (145), but represent a most promising, and perhaps the closest, approach thus far to the demonstration of direct inhibition at the unit level. If inhibition can be brought about by subliminal excitation at the same or at a different locus, from simultaneous or subsequent excitatory influx [cf. (3)], the broadest consequences will result for theories of impulse generation in a postsynaptic unit (see below, p. 272). It makes the suggestion tenable that conditioning is essentially the same whether over the same path as the excitation (necessarily subsequent in this case) or over another path, namely, depressed excitability due to the refractoriness accompanying local response. The single synapse of the squid may thus be subliminally excited and show "direct inhibition," but at other times similar subliminal response creates no refractoriness but facilitation even at the shortest intervals (145).

Adding to the several other unusual junctions already known in the system, a labile, delaying, but unpolarized functional connection is reported (84) in the brain between right and left medial giant fibers, which suggests to the authors some kind of departure from a true synapse, but in the brief announcement details are not available. A similar relation exists in *Cal-*

lianassa in the first anomuran giant system to become known [Turner (85)]. This system has also typical synapses with shorter delays than are yet known in mammals—0.25 to 0.35 msec.

In a continued study of another favorable junction in crustaceans, that between nerve and muscle, Wiersma & Adams (86) have shown the possibilities resulting from quantitative differences in amount and time course of facilitation at different junctions. Certain motor fibers fail to elicit muscle response when impulses arrive at a low frequency evenly spaced, but elicit good response when the same number of impulses per second arrives in closely spaced pairs. Other endings are insensitive to such temporal pattern and some single motor fibers seem to have both types of endings. The authors point out that this mechanism would permit, for example, two modalities of sense reception to be mediated in the same sensory fiber.

Roeder & Weiant (87) have found that insect neuromuscular junctions are like crustacean insofar as the muscle action potential is the sum of local potentials, similar to vertebrate endplate potentials, with many endings of a single motor nerve fiber on each muscle fiber of the whole muscle. Katz (88) has provided an excellent review of the earlier knowledge of neuromuscular transmission in invertebrates. Here occur, awaiting elucidation, direct peripheral inhibition, several kinds and loci of facilitation, marked independence of muscle action potential and contraction, and several types of contraction in the same muscle fiber.

The extreme, no doubt, of independence of muscle action potential and contraction has recently been found in the flight muscles of flies where Pringle (89) has discovered an utterly unexpected answer to the old question of innervation of muscle which beats many hundreds of times per second. Five or six motor nerve fibers innervate the whole of a large indirect flight muscle. Each nerve fiber carries impulses resulting in large muscle action potentials about three times per second during flight while the muscle is contracting several hundred times per second. The former is apparently necessary to put the muscle into an excitable state, when stretch (from antagonist or, for the gyroscopic haltere, from hinge elasticity) becomes the adequate, direct and rhythmic stimulus to every muscle fiber. The frequency of wing beat is thus not reflexly determined, but is a function of the peripheral mechanical properties of the system. Roeder (90) confirmed these general relations for specialized insects, adding that reduction in wing load not only raises contraction frequency but lowers action potential frequency, suggesting nervous feedback determined by the amplitude of the oscillation. When the potentials cease, contraction tapers off rapidly in amplitude and flight ceases. Generalized, slow flying insects (such as the roach and moth) show conventional 1:1 relation between potential and wing beat.

Another pregnant approach to normal fluctuations in neuromuscular transmission is developed in a study of block and fatigue in repetitively excited nerve-muscle preparations (91). Progressive partial block ("missing") of nerve impulses is apparently a quite normal event and depends only upon

the total number of impulses that have passed, not upon their frequency or the duration of stimulation. The results seem at present to be compatible with the notion that the main events in fatigue occur postsynaptically (50).

It is worth emphasizing that many of these nerve-muscle junctions whose properties are becoming known are actually performing functions usually associated with the central nervous system, that is, they are doing peripheral integration: their input-output function is departing from 1:1.

Besides peripheral neuroeffector junctions which are not 1:1, we are becoming more aware of central junctions which are 1:1, that is they perform no integrative function whatever [unless in life they experience the fatigue which we find in isolated preparations and which can bring about facilitation (83, 85, 145)]. The meaning of such relay junctions has been the subject of speculation (92). They are probably not primitive but derived as specialization from integrative ones. Stages in the process are probably represented by the slightly integrative synapses in the roach [Roeder *et al.* (93)] and crayfish [Prosser (94)] which are very similar to those in vertebrate sympathetic ganglia. Lloyd & McIntyre (95) describe an almost pure relay in Clarke's nucleus of the spinal cord and contrast it with the endings of the same muscle afferents on motor cells where more summation is necessary for transmission. Probably the most primitive junctions known, phylogenetically, are the highly integrative ones between neurons and between neuron and muscle in coelenterates (96, 97). A new artificial synapse has been described consisting of single nodes of two isolated toad fibers lying in the same saline pool [Tasaki (98)].

One other broad front of transmission physiology may be recognized, namely, the question how does the input affect the output. There have existed in the literature for many years at least two ideas which have come increasingly into focus and are more or less directly the subject of several interesting contributions this year (3, 99, 100, 101). Gesell adduces evidence in favor of a concept that the generation of impulses in a postsynaptic unit is determined directly by the intensity and rate of change of current flowing between poles of the neuron, this current in turn being influenced by internal and external factors including arriving impulses. This is in contrast to a concept, more clearly formulated by Gesell than by its presumed protagonists, wherein impulses are transmitted individually according to the ability of the postunit. Something of this kind is supposed to underlie the large literature on postsynaptic effects of synchronized input volleys (3, 102, 103, 104). Gesell argues that impulse transmission as opposed to generation *de novo* must encounter such obstacles as (a) maladaptive spread of the impulse from the locus of individual synapses antidromically up neighboring dendrites, clashing with others just out of step, (b) block by collision of all impulses except those originated near the axon hillock, (c) probable inputs of many impulses per second at each of up to 10^6 synapses on a single cell, and (d) recurrent collaterals 25 micra long which would return an impulse to the cell in 0.25 to 2.5 μ sec. The positive evidence available [see (99) for literature,

and also (105)] and the schemata are cogent and deserve more widespread attention and experimental attack. A major deficiency in the concept thus far seems to be neglect of the possibilities introduced by the local subliminal response. While retaining a sensitivity to over-all potential gradient, the cell may transmit individual impulses, may integrate many impulses, introduce its own rhythmicity, summate rather than clash neighboring synaptic effects, even be inhibited by the same mechanism (see above, p. 269), since it is known that local response may leave refractoriness or may be without refractoriness in the same preparation (145). Some picture of this sort also fits much better that great majority of animals where monopolar neurons dominate and impulses are not generated in the cell body but in the synaptic fields in the neuropile. The crayfish studies of Wiersma (83, 84, 86) are an excellent case in point. It also harmonizes with the facts on impulse initiation in nerve fibers where local delays, one-way initiation or block, death and rebirth of impulses beyond a block, many-to-one after-discharge from a small locus, rapidly fluctuating excitability, and facilitation of rate of breakdown all occur and correlate with local response behavior (46, 49, 50). It is, accordingly, of real interest that evidence is now cited in favor of the belief that normal excitation of retinal ganglion cells by bipolars is not by discrete all-or-none impulses but by a graded, summing effect resembling the local response (106).

A most significant recent development with respect to the normal mechanism of initiation of impulses is the analysis of the simple Pacinian corpuscle by Gray & Malcolm (107). Mechanical deformation of 0.5μ will excite and a nerve impulse appears after 1.5 msec. Stimuli above this threshold level produce impulses with latency as short as 0.5 msec., about as short as the shortest known synaptic delays. Moreover, subthreshold mechanical stimuli produce definite facilitation of electrical test shocks (suggesting local response). These and other properties described⁷ are all regarded as explainable by the known properties of axons, making unnecessary the assumption of receptor cells in the corpuscle. If this is not peculiar to these corpuscles, but generally true of those sense organs heretofore regarded as requiring intermediation of "true or secondary sense cells" (taste buds, ear, etc.), then the receptive structures of the animal kingdom may be more nearly unified. Although primary sense cells suffice for all types of reception in invertebrates and many in vertebrates (e.g., vision, olfaction), it has been said (108), that the latter group has become dependent upon secondary sense cells not found elsewhere. Perhaps it will develop that these are as accessory as lenses, tympanic membranes, or insect hairs.

Analysis of transmission in the central nervous system of vertebrates is still chiefly limited to the spinal cord. Marshall (109), however, has given

⁷ Lately these workers have applied linearly rising mechanical pulses of various rates of rise to measure accommodation of the receptor. Both in frog skin touch receptors and in cat Pacinian corpuscles, the values obtained are essentially those for electrical stimulation of the nerve (155).

some features of the excitability cycle of projection and cortical neurons in the geniculate-striate system. Facilitation operates on both threshold and subthreshold processes, recruitment is greater for weak stimuli and in subnormal phase. The sequence of asphyxial effects suggests that block occurs first at the axon hillock of cortical neurons, then moves into the dendrites, then into the next neuron upstream, the geniculate projection neuron, affecting terminals in the cortex before the parent axon, repeating the steps in the geniculate. Somewhat similar partitioning of the neuron in the cord was found by Lloyd (110) by asphyxia and by Barakan, Downman & Eccles (102) by analyses of potentials set up in a motor nucleus by antidromic stimulation.

Brooks *et al.* (103) analyze after-potentials and excitability in similar conditions, give the time course, and attempt to localize on the neuron the subnormality and positive after-potential. They clear up an equivocal literature by showing that after-positivity of motoneurons themselves definitely correlates with depressed excitability of monosynaptic reflexes, even following application of weak or subliminal orthodromic conditioning volleys [(104), see also (111, 112)]. Bonnet & Bremer (113) enumerate the possible sites of block in synaptic transmission and some probable signs by which each could be recognized; on these grounds they find that the block is due to lowering of synaptic potential [*contra* Brooks & Eccles (114)].

To this reviewer the new evidence increases the probability of the hypothesis that transmission depends upon electrical activity between units and upon chemical reactions, especially those involving acetylcholine, within the pre- and the postsynaptic units [see (50) and p. 275].

Rosenblueth, Wiener, Pitts & Garcia Ramos (115) have set up equations for input-output curves with which various assumptions about synaptic organization can be tested as experimental values become available. Shimbel (116) has also surveyed mathematical expressions of input-output problems. Yamigawa (117, 118) has produced a model of the synapse by modifying Lillie's iron wire experiment, in which all grades between reciprocal and irreciprocal transmission can be found, as well as delay. An unlikely application to the neuron is made by predicting that the cell body will be found to be insulated from the medium except at its poles.

ROLE OF ACETYLCHOLINE

The only unified theory now current of the physiological meaning of acetylcholine in excitable tissues, namely, that it everywhere plays a crucial role in the production of the impulse by intracellular release and destruction in conducting nerve and muscle fibers as well as at junctions, has not yet been widely accepted. There has not yet appeared a comprehensive criticism proposing alternative interpretations of the truly enormous variety of facts that have been marshalled by Nachmansohn and his collaborators (119, 120, 121). Crucial experiments have been reported to give results incompatible with the basic theory (e.g., that conduction can occur after complete inhi-

bition of cholinesterase) but in each case methodological objections to acceptance of these results have been raised and not answered. The literature has been reviewed earlier (120, 122, 123). Proper scientific caution is taken by some authors to mean that the burden of proof lies on one side, by others on the other. This reviewer is impressed by the large, positive, and unchallenged body of evidence for the theory and by the failure of essential attacks delivered to date. Much useful information has resulted from these tests. It is important to know, for example, that a significant fraction of cholinesterase exists outside the nerve fiber, as can be concluded from the finding that intact nerve destroys acetylcholine in the solution around it (124, 119), but in face of direct evidence that N¹⁵-labeled acetylcholine is absent in extruded axoplasm of fibers soaked therein (125), the essential impermeability of the axonal membrane to this ester, and therefore its normal intracellular role, cannot yet be questioned.

The most recent positive evidence has also to do with permeability. It is shown (12, 126) that sodium entry, now regarded as all-important for the impulse, is enhanced reversibly by temporary inactivation of cholinesterase suggesting that acetylcholine normally acts in impulse generation by interfering with the sodium pump which maintains the resting low inside concentration. With ion migration now known to be confined to loci millimeters apart in nodal fibers, it would be of interest to look for the pumps and for cholinesterase localization in nodes.

Recent studies reopen the old question as to whether anticholinesterase drugs have other effects which might explain *in vivo* results (127, 128). The authors conclude "that DFP and TEP disturb function by mechanisms independent of the simple inhibition of cholinesterase. An interference with oxidative metabolism is indicated." It is clearly shown *in vitro* that other mechanisms (e.g., dehydrogenases) are affected and that respiration is depressed *in vivo* but both at much higher drug concentrations than is cholinesterase. The interpretation leans on the argument that diverse thresholds for different drugs and diverse symptoms in the organism mean different points of attack in the cell, an unnecessarily involved assumption when differences in accessibility of parts of the nervous system may, on a common mechanism, mean such complex difference in site and sequence of action (129). On the other hand, the positive evidence that anticholinesterase drugs of widely different structure all give close correlations between degree of inhibition of cholinesterase and depression of electrical activity, at least in simple systems (single fiber, electric organ), and that one drug of high cholinesterase affinity (physostigmine) can protect against another (DFP), strongly indicates the one mode of action at least as first point of attack (130).

It is interesting that there has developed a more sharply drawn difference of opinion than heretofore regarding the probability of monism or dualism or even pluralism in the role of acetylcholine in different loci. While some authors (1, 49, 119, 123, 131) emphasize the similarity of mechanism of conduction and transmission and regard acetylcholine as having the same,

purely intracellular role in both, others [Eccles (132, 133); Kuffler (134)] feel forced to assign the role of transmitter to acetylcholine at neuromuscular junctions (of vertebrates but not of crustacea!) and to doubt any essential role in spinal cord or in the fiber.⁸ According to the monist view, the diverse pharmacologic responses of autonomic and other junctions have proven to be so unsystematic, especially when invertebrates are included (135 to 140), that they are best interpreted as meaning differential rates of penetration, destruction, affinity to substrate, anatomy, milieu, and other accessory factors, possibly even true chemical differences but superimposed on a basic mechanism [see also (141, 142)].

It will be profitable to examine the reasons for Eccles' rejection of the intracellular essentiality of acetylcholine and of electrical transmission at neuromuscular junctions of vertebrates. The ester and the esterase are "so low [in sensory and postganglionic orthosympathetic nerves as compared to ventral roots] that it appears most improbable that acetylcholine metabolism is concerned with impulse propagation. . . ." It is perhaps too bold, not knowing how it acts, to say when a specific enzyme mechanism definitely present is too low to function; differences of even greater order are known among samples of nervous tissue. The possibility that anticholinesterases block by other actions has been commented on above. The claim that conduction survives complete inactivation of cholinesterase would be sufficient alone, but as mentioned above there are no measurements available that do not permit, on reasonable assumptions of safety factor (and nonessential external enzyme), sufficient surviving enzyme even after days of contact with diisopropylfluorophosphate (DFP) [shown by Boell (143)]. It is said that the concentration of DFP to block is unreasonably high, but direct measurement of the fraction penetrating the axon has been made and the minute quantities found are quite in agreement with expectation. Referring to the supposed impermeability of nerve fibers to acetylcholine it is said "this cannot hold for the activated plasma membrane, for impulses certainly cause the liberation of acetylcholine from cholinergic nerve terminals" and therefore stimulated nerve should be penetrated and blocked. But review of the literature justifies the conclusion that "so far there is no conclusive evidence that the appearance of the ester outside the cell is a physiological event" (119). The undoubted permeability of the membrane at the junction cannot be generalized to the intact fiber and no distinction can be made as yet for "non-myelinated" fibers (actually it is doubtful that any fibers lack a myelin sheath) or muscle since the anatomical identification of the acetylcholine barrier has not been made. Similarly, a weak effect of externally applied drug on the cord does not mean it plays no role or that a different mechanism operates at neuromuscular junctions where one five-hundredth the concentration is effective.

⁸ Fessard & Posternak (156), in a new and extensive review of synaptic transmission, argue skillfully for pluralism without, however, emphasizing the possibility of a fundamental mechanism in common.

Kuffler argues against electrical transmission at the neuromuscular junction (134) on the basis of some interesting new experiments. (a) Impulses blocked within 1 mm. of the junction do not produce a detectable subthreshold potential in the end plate, whereas he would expect them to do so on the precedent of effects beyond a block in nerve. However, the latter are labile, not always seen and on a new interpretation (46) require active local response of the blocked region. Even near threshold shocks at the same locus, near the nerve ending, do not elicit much response, which is only to say that the elaborate structure of the axon termination is worth something. (b) Kuffler points out that inhibition of crustacean muscle is produced [Wiersma (144)] by nerve fibers which leave no electrical sign as yet recognized, and rightly emphasizes the need of further study of this case where chemical intervention is also not yet indicated. (c) He reasons that something external, the "building up process" must last 5 msec. and occur during the refractory period of an antidromic impulse, since he finds that a nerve impulse may arrive during the rising phase of a response initiated by direct stimulus to the muscle, causing no sign until the falling phase when a local potential lasting milliseconds begins. The same sequence is clearly seen in a single synapse in the squid [Bullock (145, fig. 10)] and may be anticipated in the artificial synapse. It may be suggested that this is one more bit of evidence that the excitable mechanism and the responding mechanism are separable, with a delay between. (d) The finding that physostigmine has not yet blocked antidromic depolarization of the endplate at a time when dromic transmission is affected need not argue against intracellular endplate acetylcholine because it may simply mean that the safety factor is different for the two cases.

It seems very likely that most of the ordinary synaptic delay is not time spent in an intercellular "building up" process, but rather intracellularly in the post unit. The high sensitivity of the delay (measured from arrival of prespike in the ganglion to beginning of synaptic potential) to temperature (50, 145) does not fit an intercellular electrical or a diffusion time as well as it does chemical events in the postsynaptic membrane prerequisite to the start of active response.

Other recent findings on effects of numerous anticholinesterase drugs on endplate potential do not aid in choosing between electrical and chemical transmission; the facts are fully compatible with the assumption of an essential intracellular role of acetylcholine (133, 146). 2-methyl naphthoquinone in concentrations probably inhibiting only choline acetylase impairs conduction in nerve (147). Hillarp (148) has brought telling evidence against the hypothesis (Rosenblueth, Cannon *et al.*) that glands are innervated by endings on key effectors only, which activate the rest by diffusible transmitter. Confirming his own earlier findings of neuroeffector units in adrenal, Hillarp shows that partially denervated salivary glands fixed during maximal stimulation of the remaining innervation show active and inactive acini alternating and closely adjacent.

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SOMATIC FUNCTIONS OF THE NERVOUS SYSTEM

By G. MORUZZI

Institute of Physiology, University of Pisa, Pisa, Italy

This review covers the period from July 1949 to June 1950, but earlier works not reviewed in previous articles were also taken into account. Electrophysiological papers, to be dealt with in other chapters (1, 2), were considered only inasmuch as they contribute to problems of regional neurophysiology.

Recent literature is reviewed in several monographs, articles and lectures on spinal cord (3, 4), cerebellum (5, 6, 7), diencephalon (8, 9) and mechanism of sleep (10, 11, 12), electrical activity of the brain (13 to 18), frontal lobes (6) and suppressor areas (19), sensory integration (20), experimental epilepsy (21), and electronarcosis (22). Theoretical papers are mainly related to cybernetics (15, 23, 24), relaxation oscillators (15, 25), inhibition (26, 27), and mechanism of the neuronal discharge (28). Many technical contributions to electric stimulation with condenser discharges (29, 30) and square pulses (31 to 36), to direct current amplifiers (37) and cathode ray oscillography (38) and toposcropy (39, 40), to piezoelectric recording (41), and to stereotaxic orientation of the electrodes in animals (42) and in man (43) should be consulted. A valuable help to neurophysiology is finally given by atlases of the thalamus (44) and the brain stem (45) and by neuroanatomical contributions or reviews on the cerebral cortex (46) and the subthalamus (47) of the monkey, on thalamocortical (48, 49, 50) and hypothalamocortical (51) relationships, on retinotectal (52), cerebellar (53), and olfactory paths (54, 55).

SPINAL CORD

Proprioception and monosynaptic reflexes.—Experiments on the motor innervation of the cat's intrafusal muscle fibers suggest a spinal regulation of the mechanical "bias" of muscle spindles by independent motoneurons, discharging through small, slow-conducting axons (56). There is evidence, however, that the intrafusal and ordinary muscle fibers of the frog receive a common innervation (57). The large Group I muscle afferent fibers, after supplying myotatic reflex collaterals to the motoneurons, synapse with the cells of Clarke's columns (58); stretch-evoked discharges are recorded in the cat from the dorsal spinocerebellar tract (58) and the restiform body (59), thus suggesting that proprioceptive cerebellar reflexes are probably imposed on the monosynaptic activity of the spinal cord. Whereas the muscle afferent fibers for the most part terminate in the lower spinal segments, the large myelinated fibers arising from the cat's knee joint ascend through ipsilateral dorsal funiculi to the medulla oblongata (60).

Proprioceptive impulses elicited by muscular contraction have first a

facilitating and then an inhibitory influence on the corresponding monosynaptic reflexes (61, 62). The longer latent time of the inhibitory effect may result from its multisynaptic character (61) and the proprioceptive inhibition is probably tonic in nature, thereby accounting for spastic states (62). Multisynaptic reflex patterns are also modified by muscle afferent impulses (63) and the proprioceptive facilitation is related in the spinal frog to slow subliminar depolarization of the motoneurons (64). Muscle afferent signals converge with pyramidal discharges on the final common path, where spatial summation occurs: cortical facilitation of subliminar myotatic reflexes is found to wax and wane with a rhythm of about 10 per sec. (65).

Multisynaptic reflexes.—These reflexes are far more depressed by myanesisin (66, 67) and increased by strychnine (67) than are the monosynaptic ones; they show also little post-tetanic potentiation, which is constantly observed in the monosynaptic reflexes (68). The crossed extensor reflex (41), the ipsilateral flexor reflex (41, 69, 70), and the Türck reflex (71) were investigated. Both quick and slow units take part in the flexion reflex (41), but the slow (red) part of the tibialis anterior has the lower central threshold (72). High frequency discharges up to 300 to 400 per sec. are observed in the cat's motor nerves during the flexion reflex (69); although single motor units were not recorded, cooling experiments suggest that the discharge might occur in the same motoneuron (69). Some plurisynaptic nociceptive reflexes, such as the lingual (73) or the ipsilateral flexion reflex (74, 75), are never observed as a positive response in the normal man, although inhibition of voluntary innervation of both extensor (74) and flexor (76) muscles follows an electric shock applied to the ipsilateral hand. The long latent time and the lack of reciprocal innervation might suggest, however, suprasegmental levels of inhibition.

Miscellaneous.—Scheminsky's effect is again confirmed (77), although no changes are observed in the electrospinogram by reversing the current polarity (78), and a new electrotonic explanation of its mechanism is given (79).

Unilateral extirpations, in mammals and birds, of cerebellar lobuli (80, 81, 82), motor cortex (83, 84) and vestibular apparatus (85), as well as prolonged unilateral strychninization of the cerebellar cortex (86), are followed by asymmetrical activity of the spinal motoneurons. The asymmetry persists after total spinal transection (80 to 86) and complete deafferentation of the caudal segments of the spinal cord (80), thereby suggesting (a) an automatic activity in the isolated segments of the spinal cord and (b) a long persistence of the functional changes evoked by previous asymmetric innervation from higher centers (80). The activity of the spinal neurons is thus determined also by their history.

Chronic experiments on the mechanism of spasticity following short lasting spinal hypoxia (87), on the cutaneous hyperirritability produced by application of alumina cream above the dorsal aspect of the lumbar enlargement (88), and on the lack of regeneration in the spinal cord of the rat (89) close this list of contributions to spinal physiology.

LOWER BRAIN STEM

The brain stem reticular formation.—This mechanism controls both spinal and cerebral mechanisms through descending and ascending pathways.

The spinal sphere of influence was thoroughly investigated in the past years [see (90)] and the recent addition of information concerns the selective depression by myanesin of Magoun's centers (66, 67), the positive potentials elicited in motoneuron pools by the spinal relays for reticular inhibition (91), and the bulbar inhibition of spinal inhibitory reflexes (92).

The influence on the cerebral cortex is one of activation or desynchronization (93). Whenever reticular stimulation is applied against a background of cortical synchrony in an "encéphale isolé" preparation, Berger's alpha blockade and the electroencephalographic arousal reactions elicited by sensory stimulations are easily duplicated. The whole central core of the brain stem, extending from the bulbar reticular formation forward through the pontile and midbrain tegmentum into the caudal diencephalon, has a diffuse influence on the cerebral cortex, through paramedian multineuronal chains of ascending reticular relays (93). The slow cortical waves in full chloralose anaesthesia, the cortical and intralaminar recruiting potentials elicited by low frequency stimulation of thalamic diffuse projection systems are also abolished by the ascending reticular discharges, whereas strychnine spikes and chloralose responses to sensory stimuli are unaffected (93). The possibility is put forward (93) that the cortical arousal reaction is mediated by collaterals of afferent pathways to the brain stem reticular formation and thence through the ascending reticular activating system, rather by intracortical spread following the arrival of afferent impulses at the sensory receiving areas of the cortex.

This hypothesis is substantiated by the fact that the electroencephalographic sleep patterns of the "cerveau isolé" (94) are duplicated by acute lesions in the midbrain tegmentum or in the hypothalamus interrupting the ascending relays of activating reticular neurons; whereas acute injury to lateral midbrain areas, blocking the medial and lateral lemnisci and spinothalamic tracts, as well as subsequent bilateral section of optic nerves and destruction of olfactory bulbs, do not precipitate sleep patterns (95). These findings may be regarded as conclusive evidence that the ascending influence of brain stem reticular formation is tonic in nature and may account for earlier observations of lethargy following encephalitis, diencephalic tumors and brain stem lesions [see (96)]. After a chronic lesion of the midbrain tegmentum or hypothalamus, sparing sensory connections to cortex, the animals appear asleep, but short lasting electroencephalographic activation is still induced by strong sensory stimulations (97), thereby showing that wakefulness and cortical arousal reaction are overwhelmingly but not exclusively related to the ascending reticular system.

Miscellaneous.—The receptors for tonic neck reflexes have been localized in atlantoaxial and occipitoatlantal joints (98); the interrelations between cervical, ampullary, and otolithic reflexes have been investigated (99, 100, 101) and the frequency of the response of the extraocular motoneurons to

labyrinthine stimulation has been determined (102). Postural tremor results in monkeys from lesions to the ventromedial midbrain and pontile tegmentum and to the cerebellar nuclei (96); the best decerebrate rigidity is produced in cats with combined lesions of superior vestibular nuclei and of medial reticular formation (103). The lateral reticular nucleus (104) and the inferior olive (105) have been suggested as relays in the transmission of exteroceptive (104) and extrapyramidal (105) impulses to the cerebellum. The brain stem structures responsible for movements of the head have been localized (106) and the course of spinothalamic and medial lemniscus paths has been mapped (102).

The following problems of comparative physiology have been investigated: distribution of eye muscle spindles (108) and of related proprioceptive discharges (109) in mammals, fear reactions to visual stimuli of thalamic and hemidecerebrated pigeons and influence thereon of local applications of strychnine on the optic lobe (110, 111), the effect of *d*-tubocurarine (112) on the optic lobes, the electric responses of the midbrain tectum to optic impulses in lowest vertebrates (113), demonstration of an avian homologue to the pontine gray projecting to the cerebellum (114), and stimulation of electric lobes in *Torpedo marmorata* (115).

CEREBELLUM

Inhibition.—The pathways for cerebellar inhibition have been determined (116). Cortically-induced movements are inhibited in the cat at spinal levels (116, 117) through fastigioreticulospinal paths (116), by stimulating the anterior lobe (116, 117), the paramedian lobuli (116) and the fastigial nuclei (116). The same paths are utilized for the cerebellar inhibition of spinal reflexes and of postural tonus (116), whereas midbrain relays are reported to be unessential for inhibiting decerebrate rigidity (118). Thus, cerebellar (116) and cerebral (119) impulses converge on the reticular formation, whose suppressor centers might be regarded as the final common path for the inhibitory systems of the mammalian brain. The clonic movements, elicited by local strychninization of the optic lobes in the acute thalamic pigeon, are also inhibited by cerebellar stimulations (120, 121).

The cerebellar inhibition is tonic in character, at least in lower mammals (122) [see (5)]. The following experiments, made on decerebrate preparations, suggest that proprioceptive impulses arising in the hindlimbs inhibit, through cerebellar relays, the postural tonus of the forelimbs and vice versa: (a) atonia of deafferented forelimbs is converted into rigidity by extirpation of the anterior lobe (123); (b) the same result is obtained by spinal transection at a thoracic level (123) or by hindlimb deafferentation (124), and then no further increase of rigidity is produced by extirpating the anterior lobe but flaccidity is at once restored by ipsilateral labyrinthectomy (123); (c) forelimb deafferentation increases rigidity of previously deafferented hindlimbs (125). The implications (123, 124) are really challenging: since the Schiff-Sherrington effect is considered as a release from cerebellar inhibition, Sherrington's atonia of deafferented limbs is regarded merely as a consequence of

the cerebellar inhibition of labyrinthine tonus and the rigidity of deafferented limbs after Pollock and Davis' decerebration is explained by anaemic inactivation of the anterior lobe [see (5, 7)]. The following problems are open to future investigation: (a) the Schiff-Sherrington effect, i.e., increase of forelimb rigidity following thoracic transection, is not abolished by previous deafferentation of all caudal lumbosacral segments (126, 127); (b) strong bioelectric activity is still recorded in acutely (128) or chronically (59) isolated cerebellar areas; and (c) rigidity in deafferented forelimbs, resulting from hindlimb deafferentation, has been observed in chronic decerebellate animals (129).

Facilitation.—Facilitation of spinal reflexes and of cortically induced movements is easily obtained in monkeys from areas yielding inhibitory responses in the cat (130). Although inhibition predominates in lower mammals and birds, concealed facilitating components are suggested by the strong rebound response (5, 131) and actually increase of decerebrate rigidity (132, 133, 134) and facilitation of cortical movements (117, 130) have been observed during electrical stimulation of the anterior lobe of the cat. Finally, decerebrate rigidity (135) and myotatic reflexes (136) are increased instead of being inhibited if the frequency of stimulation of the cat's anterior lobe is reduced from 300 to 50 per sec. to 10 to 5 per sec. (135), whereas the opposite result has been recorded in primates by investigating the influence of rate of cerebellar stimuli on cortically-induced movements (137). For details and full discussion of these results, recent surveys should be consulted (5, 6, 7); differences of species and of background may account for partially conflicting reports.

The site of cerebellar facilitation of cortically-induced movements (Rossi effect) is controversial. Neocerebellar facilitation (138) occurs at cortical levels and is mediated through the superior cerebellar peduncles (139). Facilitation from the anterior lobe of the cerebellum (117, 130) is however mediated through the nuclei fastigii and possibly the inferior cerebellar peduncles (130); since spinal reflexes are also increased, bulbospinal mechanisms of facilitation have been postulated (130). However, electroencephalographic activation is brought about by stimulating the fastigial nuclei and the bulbotectal formation (93), suggesting that cortical levels might be activated through the juxtarestiform body and the ascending system of reticular relays (see section on the lower brain stem). Of course, conjunctival paths [see (140)] might be involved as well.

Localizations.—Anatomical (141) and physiological (142) evidence confirms earlier findings on somatotopic geography of the anterior lobe. A slight overlap is suggested by the results of localized lesions (143) and a spread of inhibition results from increasing the rate of stimulation of the anterior lobe of the cat. High frequency pulses (up to 300 per sec.) are most effective for inhibiting decerebrate rigidity (135) and cortically-induced movements (116). Inhibition of decerebrate rigidity may be localized to the corresponding ipsilateral limb if threshold voltages at the rate of 50 per sec. are applied to the culmen; ipsi- and contralateral spread of inhibition occurs, however,

if the frequency is increased to 300 per sec., the voltage and the duration of single pulses remaining the same. This bilateral spread is not prevented nor decreased by sagittal splitting of the anterior lobe and further insulation, thus suggesting a synaptic spread of inhibitory impulses at fastigial or bulbar levels (142).

Electrophysiology.—Spike discharges are easily recorded within the cerebellar cortex and their intrinsic origin is proven whenever high frequency outbursts are produced by local strychnine and when long, easily fatigued after-discharges are observed following sensory stimulation (59, 144). In the decerebrate cat, the frequency of "rest" discharge of intrinsic units, i.e., neurons having their somata within the cerebellar cortex, is surprisingly high, averaging around 150 per sec. (59, 144), i.e., of the same order of the frequency of the cerebellar waves recorded with coarse electrodes; it is increased up to 400 to 500 per sec. by local strychnine (59, 144), which instead evokes a low frequency (10 to 30 per sec.) synchronization of the cerebellar waves (145).

Spike potentials of single cerebellar neurons superimposed upon a baseline of typical cerebellar waves are recorded from the granular and Purkinje layers, but not from the molecular layer or the underlying white matter (146); the thin unmyelinated axons of the molecular layer are, of course, unsuited for unitary recording of spike discharges, but if the molecular fibers are synchronously activated by electric stimulation, transynaptic responses of Purkinje neurons are recorded near or in their dendritic processes, i.e., in the molecular layer itself (147). The spike discharges are more sensitive than the cerebellar waves to anaemia or ether (146).

Miscellaneous.—Facilitatory (67) and inhibitory (66, 67) responses to stimulation of the anterior lobe are selectively abolished by myanesin and the extreme rigidity which follows extirpation of the anterior lobe in the decerebrate cat is depressed by myanesin (148) and apomorphine (149), but is left unmodified by doses of morphine clearly decreasing decerebrate rigidity (150). Otolitic reflex upon eye movements are strongly affected in the guinea-pig by histologically-controlled lesions of the flocculus (151).

DIENCEPHALON

The mammalian thalamus consists of two divisions, i.e., specific projection system and diffuse projection system (152). The specific systems project to localized cortical areas, whereas the diffuse or reticular system has widespread cortical projections. Physiologically, both intralaminar nuclei and nucleus reticularis belong to the diffuse projection system (152), although the intralaminar nuclei project to the rhinencephalic cortex (48) and belong therefore, anatomically, to the specific projection systems.

Reticular system.—The multisynaptic nature of the reticular system is substantiated (a) by the long latency (15 to 60 msec.) of the cortical recruiting responses (152) and (b) by the recruitment itself. The nucleus reticularis has been suggested as an intrathalamic relay in the thalamocortical paths responsible for the generalized recruiting potentials evoked by stimulating

the intralaminar nuclei (48). Waxing and waning of cortical (153) and subcortical (154) recruiting responses, and the influence thereon of local co-cainization and asphyxia (154) show that the recruitment occurs both at cortical and thalamic levels. The response spreads contralaterally through the intralaminar nuclei (93), involving also striatal centers and hippocampal areas (152). The influence of the diffuse projection system on the spontaneous electric activity of the brain will be dealt with elsewhere (1) [see (95, 152, 155, 156, 157)]; its physiological significance is shown by the remarkable coincidence between electroencephalographic responses and behavioral effects of thalamic stimulation in freely moving unanesthetized cats (158). Generalized recruiting responses are produced only with low frequency stimulations and by increasing the frequency of the stimuli above 30 per sec. activation patterns with low voltage fast activity are observed instead. A parallel reversal in animal's behavior has been found by changing the frequency of thalamic stimulation (158). Hess' sleep reactions are duplicated with the lowest rate of stimulation (3 to 5 per sec.); higher frequencies (10 to 30 per sec.) evoke the arrest reaction, which is characterized by a sudden arrest of all spontaneous activity, whereas still higher frequencies (200 per sec.) evoke activation patterns, which may appear as outbursts of "sham rage" when the inferior portion of the massa intermedia is stimulated. Facilitation of cortically-induced movements is yielded by a wider area and is not strictly related to cortical activation (152, 159). Hess' previous findings on thalamic massa intermedia [see (8)] are thus confirmed and explained, although the sleep occasionally produced by midbrain stimulations (8) could hardly be attributed to recruiting responses. It is most significant, however, that thus far arrest reactions have been obtained only from thalamic regions yielding recruiting responses (158). Thus, the widespread synchronization of the recruiting potentials parallels behavioral manifestations suggesting an impairment of awareness, and the hypothesis has been put forward that the diffuse projection system "may be involved in the 'higher level' integrations of cerebral activity related to mechanism of attention, consciousness and general alertness" (158).

Specific projection system.—The repetitive cortical discharges following afferent stimulation are still observed after destruction of the thalamic massa intermedia; they occur simultaneously in the cortical sensory areas and in the corresponding nuclei of the specific projection system and depend upon the integration of the two structures by their fiber connections (160). Corticothalamic reverberating circuits (160) and tonic reciprocal facilitation between cortex and thalamus (155) have been put forward as possible explanations for these long lasting sensory after-discharges. No sharp localization of the representation of the body surface within the ventral posterior thalamic nucleus has been observed (161) and the thalamic relay nuclei for the second sensory receiving areas of the cerebral cortex have been localized (162).

Subthalamus.—Localized chronic lesions in Luys' subthalamic nucleus are followed in monkey by specific symptoms of choreoid hyperkinesia,

which are decreased by medullary section of pyramidal or rubrospinal tracts and might be explained with a disorganization in the pallidal influence on motor cortex and rubral nuclei (163). The efferent connections of the cerebral cortex with diencephalic and striatal nuclei have been determined anatomically (164) and physiologically (165).

CEREBRAL CORTEX

Visual areas.—The latency of the early cortical response to visual stimulation and the retinocortical time have been measured in man (166); although the first volley of retinal impulses arrives only 40 msec. after the flash, the alpha blocking time (215 ± 45 msec.) is much longer, suggesting a quite different, multineuronal mechanism of activation [see (93)], not necessarily involving intracortical spread from visual projection areas [see also (167)].

Auditory areas.—The primary, second, and third acoustic areas have been investigated in the cat (168 to 172). The first auditory field can be identified in cytoarchitectonic terms (171) and is the only one activated directly by medial geniculate impulses (171); the second acoustic area is activated by impulses arising in the first auditory field; reverberating effects are sometimes observed in the first auditory area after local strychninization of the second acoustic field (172). The results of a complete electrophysiological analysis of the central auditory pathways, from the medulla to the secondary cortical area, should be read in the original article (173). The cortical projection of vestibular nerve (174) and the combined effects of unilateral labyrinthectomy and cortical ablations (175) have been investigated.

Olfactory and taste areas.—Activation patterns are produced in the rabbit's olfactory bulb by natural stimuli (20, 176). Although the disappearance of slow waves is caused in the first instance by desynchronization, this might lead to a fall in activity, through a decrease of the ephaptic forces resulting from the disorganization of the beat. Thus, whenever large masses of cells stop beating in unison, as in the alpha blockade, a reduction of the number of active units ensues, simulating inhibition (176). Neuronographic analysis (177) and ablation experiments (178) suggest that the rhinencephalic cortex transcends its role of olfactory area and participates in the mechanism of mammalian behavior (178). The cortical areas for taste impulses have been mapped (179).

Somatic afferent areas and motor cortex.—Muscle afferent impulses modify the frequency of strychnine spikes in the contralateral sensory-motor cortex (180). The sensory potentials are blocked by curare (181) [see however (182, 183)], and are strongly influenced by barbiturates (184). The importance of the inflow of somesthetic impulses on the activity of the motor cortex is proven by physiological (185) and anatomoclinical evidence (50). The iterative nature of the pyramidal system is substantiated in barbiturized cats, by stimulating the motor cortex and the corticospinal tracts (186), and the selective effects of the frequency of stimulation (187, 188, 189) are explained with different rate of temporal summation of pyramidal impulses at bulbospinal levels (187). Blocking of the precentral beta rhythm, which characterizes the activity of resting motor cortex, is observed in man at the

beginning and at the end of voluntary movements (190). Facilitation and deviation are observed in the motor and in the sensory responses of human pre- and postcentral gyri to electric stimulation (191). Pattern of localization in the primate precentral cortex show overlapping of motor areas (193, 194), which might account for the recovery following small cortical lesions (194). Homotopic and heterotopic interrelations between the motor gyri of the cat are mediated by callosal fibers (195), whose degeneration sensitizes cortical neurons (196). Somatic and suppressor responses have been elicited from autonomic areas in the posterior orbital (197) and in the anterior cingulate (198) gyri and the influence of bulbocapnine (199) and anemia (200) on cortical and subcortical centers has been investigated.

Suppression and Leão's depression.—These are identical phenomena, spreading corticocortically and requiring no neural continuity but only physical and neural contiguity for their spread (201). Suppression of thalamo-cortical activity does not occur at the thalamic level, since after isolating and insulating a cortical area no electrical silence is anymore observed in the corresponding thalamic region, thereby showing that thalamic suppression was "secondary to the reduced cortical activity of its projection area" (201); similarly, in Leão's phenomenon, thalamic nuclei are invaded successively as depression spreads to the corresponding cortical areas (202). The intracortical spread is probably ephaptic in nature (201), whereas the secondary corticothalamic spread is apparently related to synaptic transmission (201, 202). Four types of electroencephalographic spreading depression are described (201), the fourth being characterized by "convulsoid" activity spreading at the same rate as the pure depression (203) and showing striking resemblance to one mechanism of spread of epileptic discharge (201). The physiological meaning of these phenomena is controversial: cooling and superficial drying are not prerequisite (201) but important factors (201, 204) for its initiation, dial anesthesia facilitates spreading depression (205), but positive (201) and negative (206) findings are reported in the unanesthetized animal. Cortical inhibition of spinal and diencephalic activities is, of course, not disproved by these new findings and the frontal lobectomy has just been found to increase in dogs the reaction to restraint without facilitating the appearance of rage (207). However, the electroencephalographic changes following sciatic stimulation, which had been ascribed to reflex activation of suppressor areas (208), might be reinterpreted as activation patterns. Reduction of active units, brought about by desynchronization (176), and decrease of intrinsic cortical activity, resulting from chloralose anesthesia (157), might explain recent findings (93) in which suppressor-like electroencephalographic patterns were evoked during arousal reactions.

MISCELLANEOUS

Conditioned reflexes.—Prefrontal areas (209), including the suppressor band 8S, and the reticulospinal tracts (210) are essential for negative conditioned reflexes in the dog. Although olfactory receptors appear to function at birth, conditioned reflexes are elicited only after three weeks (211). Subliminal conditioned reflexes, influencing electroencephalographic patterns but

yielding no effector responses, have been obtained in man (212). Conditioned photic reflexes are less easily produced in fishes after cerebellar ablation (213). The conditioned reflexes involved in swimming have been analysed (192).

Electronarcosis.—Electronarcosis, from interrupted D. C. stimulation, is characterized by suppression of electric activity in spinal cord (214), cerebellum (215), and cerebral cortex (216). The spinal silence is due to reflex inhibition from a diencephalic center, since the effect is abolished by severing the spinal cord rostrally to the stimulating electrodes or by destroying the center (214). A surprisingly long suppression (20 to 30 min.) of the cerebellar waves is produced by stimulating the region of the mammillary bodies (215). The cortical (217, 218, 219) and the cerebellar (215) silences (extinctions), following local application of square waves (215, 217, 218) or faradic stimuli (219), are also believed to be the consequence of reflex activation of diencephalic or brain stem inhibitory centers. However, stimulations of the cerebellar anterior lobe or of bulbar inhibitory centers, yielding complete and long lasting suppression of postural tonus and of myotatic reflexes, are never followed in the intercollicular cat by cerebellar silence; much stronger stimuli are required for evoking only a short lasting extinction (220).

Experimental epilepsy.—Experimental epilepsy, repeating motor and EEG clinical patterns, is caused by strong stimulation of thalamic intralaminar nuclei (158). The electroshock convulsion is, instead, an epileptic after-discharge, following a strong, short lasting but thoroughly nonlocalized stimulation: the convulsive patterns are here distributed almost everywhere in the brain and are constantly recorded from the cerebral cortex during the "tonic" phase of the seizure (221, 222). These clear-cut experiments, as well as recent findings showing that deafferentation, alone (223) or followed by section of the eighth nerve (224), never prevented "tonic" convulsions, definitely dispose of the time-honored hypotheses of the subcortical and eventually postural mechanism of the "tonic" phase of the epileptic seizure.

Jacksonian epilepsy is elicited in the unanesthetized rabbit (225) by tactile stimulation of mouth receptors after local strychninization of the cortical masticatory area (Amantea's epilepsy), or by photic stimuli after strychninization of the area striata (Clementi's epilepsy). The spread of the electroencephalographic epileptic patterns from the strychninized visual area to the normal masticatory cortex is facilitated by visual stimuli and by tactile stimulation of mouth receptors, but is not prevented by their local anesthesia (226) or by bilateral section of the optic nerves (227). Clementi epilepsy is furthermore abolished by diphenylhydantoinates (228), whereas Amantea's epilepsy is unaffected, if no spread to unstrychninized cortical areas is involved (229, 230). Amantea's epilepsy is potentiated by local application of prostigmine (231) and sodium phosphate (232). Atropine doses leaving Amantea's and faradic epilepsy unaffected, prevent the Jacksonian seizure resulting from local application of acetylcholine on the rabbit's masticatory cortex (233); these findings and the effects of diisopropylfluorophosphate [(234, 235); see, however (236)] suggest that cortical accumulation of acetylcholine is not adequate by itself for producing seizure patterns.

No epileptic potentials are recorded from the cerebral cortex during generalized convulsions following cerebellar stimulations (237), intravenous acetylcholine (238), and ammonium chloride (239), as well as in Brown-Séquard "epilepsy" (240). Epileptic after-discharges following electrical stimulation are decreased or abolished by barbiturates and diphenylhydantoin (228), by myanesin (67), and by carbon dioxide (241); the inhibition of cryoepilepsy by carbon dioxide in the frog is not related to lowering of the blood pH (242). Epileptic foci are fired by local metrazole, which is ineffective in evoking convulsive "spikes" in the normal human cortex (243).

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THE ELECTRICAL ACTIVITY OF THE BRAIN

BY HENRI J. GASTAUT

Laboratoire de Neurobiologie, Faculté de Médecine, Marseille, France

From June, 1948 until June, 1950, the period covered by the present review, the outstanding development of electroencephalography (EEG) is shown by a certain number of important facts: for example, it was chosen as one of the themes of the Fourth International Congress of Neurology with Bremer (1), Jasper (2), and Hill (3) as rapporteurs, and it has been the subject of the reports of Jung (4) and Gastaut (5) to the Congress of the "Deutsche Gesellschaft für innere Medizin." The Twelfth International Congress of Psychology has attached a certain importance to it (7), and the First International Congress of Psychiatry reserves one morning for the discussion of a report on EEG in Psychiatry.

The Second International Congress of EEG was held in Paris in September, 1949 with 48 communications, six reviews presented by Brazier, McCulloch, Gastaut, Jasper & Walker, Rémond, Dreyfus-Brisac & Laporte, and Walter, and four lectures delivered by McCulloch, Jasper, and Penfield (8, 9). The Third International Congress of EEG has been arranged for September, 1952 in Boston.

National meetings have been held once or twice a year in countries in which there exists a National Society of EEG: England, United States, France, Spain, Italy, Belgium, Holland, Sweden, Denmark, Switzerland, and Japan. The papers of these meetings are sometimes published in national scientific periodicals and are always abstracted in the new journal, *EEG and Clinical Neurophysiology*, which made its first appearance in 1949. Judging by the quality and high scientific standard of this journal, its future is assured. This journal is the official organ of the International Federation of EEG and Clinical Neurophysiology (10) which was founded in September, 1949 by the joint action of the various national societies. The headquarters of the Federation are at present in Marseille.

Two treatises on EEG have appeared, and two small books one, by Ogilvie (11) and the other by Delay (12) have been reissued: the book by Cohn (13) represents a very personal point of view and contains only a score of references; that by a collection of British authors, on the other hand, is a large symposium containing more than 500 references with various chapters by Hill, Parr, Walter, Cobb, Whitteridge, Greville, and Heppenstall (14). A new edition of the atlas by Gibbs in three volumes is in press, as is also a treatise on clinical EEG published under the auspices of the French Language EEG Society by Baudouin, Fischgold, Gastaut, Rémond & Verdeaux (15).

In Germany and France two medical reviews have devoted a special number to EEG: the *Archiv für Psychiatrie und Nervenkrankheiten* has collaborated with the *Zeitschrift für die gesamte Neurologie und Psychiatrie* in the publication of a special number of 292 pages in commemoration of Hans

Berger (17); *La Semaine des Hôpitaux de Paris* has devoted an edition to the work of the Laboratory of Neurobiology in Marseille (16).

The rapid expansion of this subject is perhaps most vividly illustrated by the large number of papers which have appeared in the last two years. Seventeen hundred have been collected and the mere enumeration of these would take more than the space allotted to this review. For this reason, we have been obliged, for the first time since the electrical activity of the brain was discussed in this *Review*, to exclude references to purely clinical publications, which represent more than three quarters of the published work. The principle of exclusion may be accepted more readily if it is realized that, however great may be the interest of many in these papers, they reflect only indirectly the physiological point of view implied by the title of this volume.

General reviews on the electrical activity of the brain have appeared in almost all countries of the world. Those with a bias for scientific or theoretical aspects are those of Jasper (18) and of Kornmüller (19), and those with clinical and sometimes even popular appeal are numerous (20 to 55). One should also mention among the more general publications the bibliographical reviews of Walter *et al.* (56, 57) and of Barnes (58) as well as the essay on terminology by Walter (59).

TECHNICAL ADVANCES

With regard to technical progress, a book of great interest is in preparation by Walter & Shipton (60). This deals with electrical and radioelectrical technique applied to physiology and medicine.

The question of electrodes is considered principally as a function of the needs created by new techniques. Orientable cortical electrodes with a support which can be fixed upon the bone have been proposed by Geddes (61) and Curtis-Marshall (62) and have been made commercially by Grass in U.S.A. and Artex in France. Henry (63) has suggested a "postage stamp electrode" for subdural recording. Various models of pharyngeal electrodes have been utilized by Faure & Bramerie (64), Gastaut (65), Roubicek & Hill (6), McLean (66), Umlauf (67), while Alejandro & Arellano (68) have applied a tympanic electrode. With regard to surface electrodes (69, 70), an original solution has been suggested by Rémond & Delarue (71) to solve the double problem of maintaining equal interelectrode distances and equal pressure on the scalp. For subcortical recording, multilead needles were used either made by the experimenter himself (72) or as could be bought commercially, for example, the Grass needle. For prolonged stimulation during experiments, Kubicek *et al.* (73) used an electrode of a special type. From the theoretical standpoint, Grass (74) and Rouvray & Rémond (75) have studied the fundamental characteristics of different types of electrodes used in EEG, while Silver (76) recalled that the use of bentonite to attach certain electrodes can produce cutaneous reactions.

Bickford (77) and Coates (78) each described an electrode-selector, of which the latter is particularly inexpensive. King & Trufant (79) have constructed a headholder especially designed for experiments, Kaufmann &

Walker (80), a stereotaxic instrument which is both simple and inexpensive. Bartholomaeus *et al.* (81) have studied the modifications desirable in the technique of placing needle-electrodes in the brains of animals. Four stereotaxic instruments for use in human experiments have been worked out almost simultaneously in France and in America. In addition to that of Spiegel & Wyss (82) are those of Taleyrach *et al.* (83), Baudouin *et al.* (84a, 84b), Hayne *et al.* (85) and Jasper & Hunter (86).

Recording apparatus is now made commercially in sufficient quantity both in America and in Europe: England (87), France, Germany (88), Belgium and Denmark. Two models have been suggested in Italy (89, 90), Lérique (91) has made a differential preamplifier with multiple inputs and common feed-back and Offner (92) a direct current amplifier of high stability. Anderson (93) has described a simple ink-writer for mercuric manometry and Ax & Greenblatt (94) transformed, with some accessories, an ordinary EEG into a polygraph registering somatic responses. Rémond, Ubersfeld & Delarue (95) have drawn a remarkable magnetodynamic oscillograph with high frequency response. Schaefer (96) has described a simple method of calibrating the apparatus and Gordon (97) has constructed an EEG calibrator for this purpose.

The transmission of the EEG by radio has been suggested by Prast (98) with some other technical points dealing with radio problems and notably the elimination of short waves artifacts. This author (99 to 104) further utilizes a miniature preamplifier carried on the head above the electrodes and a small four-stage amplifier including a frequency modulator and an audio-oscillator. The reception is by means of a receiver for frequency demodulation of the carrier. Fuller & Gordon (105) have considered the same problem in the animal. Breakell, Parker & Christopherson (106) have been dealing with this question since 1946 and have already succeeded in sending human EEG by radio. The problem is of great theoretical interest both to physiologists and to others for it seems to offer a real prospect of studying the EEG under varying conditions in both man and animal.

The practical and clinical application of frequency analysis has been considered by Walter (107, 108) and by Cohn (109). Drohocki (110, 111) has discussed the physical bases of the method and dealt in detail with the question of filters. Minot (112, 113) has suggested a simple and easily applied method of analysis using a photoelectric frequency multiplier, but this method has a serious inconvenience in that it does not provide an immediate and continuous graphic record. Hoefer, Markey & Schoenfeld (114, 115) on the other hand, have improved the graphic representation by adding the parameter of time; but their instrument is complex and difficult to attach to other equipment and will probably remain a laboratory device. The only practical equipment at the present time remains, in effect, that suggested by Walter and it is now constructed in England by Edison Swan and in America by Offner. Prast (116) uses an automatic analysis only of the waves of the theta band of the EEG without taking any account of their amplitude. Drohocki (117) on the contrary, has been studying a quantitative analysis

using the integral of the cerebral potential. Goodwin & Stein (118) have worked with their "correlator" on phase analysis and some results of their methods have already been given by Henneman, Goodwin & Toll (119) and by McCulloch (8). The question of spatial and temporal analysis was the subject of the European Symposium on EEG which was held in Marseille in July, 1950 (120).

Toposcopy, a method of recording emphasizing a spatial distribution of potential differences on the scalp and the cortex, has been the subject of a number of researches which have resulted in the construction of four pieces of apparatus by Walter & Shipton in England (120), by Goldman *et al.* (121, 122, 123), by Cohn (124) and by Lilly (125) in the U.S.A. Walter and Goldman utilize cathode-ray tubes and Cohn and Lilly, neon-lamps. The first three types of equipments are easily used in man while the last is more in the nature of a microtoposcope which permits the exploration of one square centimeter of cortical area by 25 electrodes. The most highly developed of these instruments is without doubt that of Walter & Shipton which permits display not only of the spatial distribution of potentials but also indicates frequency, phase relations, and presence of harmonics in the waveform derived from 24 channels.

Slow-waves of 5 to 7 c.p.s., which are the first to indicate in the EEG the effect of hypoxia, are used in the anoxia-indicating and warning device of Prast & Noell (126 to 129) which is essentially a limited frequency analyser. Bickford (130) uses in men and in animals the electrical activity of the brain which varies with the depth of anesthesia to regulate the level of the latter by using a system of negative feed-back.

The assessment of hyperpnea and its effect on EEG has been studied in various ways by different authors (131). Bickford (132) and Schwab utilized quite simply the measure of ventilation while Asmussen & Buchthal (133) made separate measurements of alveolar carbon dioxide on samples of expired air. The most elaborate method is that developed by Blinn & Noell (134, 135, 136) who measure the value of alveolar carbon dioxide by infra-red analysis, a method permitting automatic and continuous registration.

The methods of activation which can provoke or increase EEG abnormalities in abnormal subjects have received a great deal of attention. Kaufmann & Watson (137) and Gastaut (138) have published a general review on this subject. The classical test employing hyperpnea as applied to children is dealt with by Debré, Lefébvre, Lérique-Koechlin & Nekhorocheff (139), while Vigouroux & Gastaut (140, 141) discuss the difficulty of interpreting the results of this method. It is indeed curious that 15 years after the introduction of this method in EEG the slow waves which it provokes in normal subjects should still be considered by certain people as pathological and even as specific to epilepsy! Sleep, both normal or provoked by seconal (142), by pentothal (143 to 146), by Nesdonal (147) or by paraldehyde (148, 149) has proved itself an activator of great value both in psychomotor epilepsy [Gibbs *et al.* (150, 151)] and in idiopathic epilepsy, as well as in cases where seizures are secondary to cortical lesions. Organic lesions affecting one hemi-

sphere produce an asymmetry of the sleep rhythms [Cress & Gibbs (152)] and suppression of the responses of the sleeping cortex to sensory stimuli [Grossman (153)].

Intravenous injection of metrazol is used as an activant by Cure, Rasmussen & Jasper (154), Roger *et al.* (155, 156), and Merlis, Henriksen & Grossman (157). From this work it seems that the best technique is to use a very slow injection of diluted metrazol. Ziskind & Bercel (158) suggest measuring in cubic centimeters of metrazol the "minimum threshold EEG," that is to say the moment of appearance of the first burst of slow waves provoked by this compound. Gastaut & Rémond (159, 160) and Gastaut (5, 8, 161, 162, 163) suggested a method of measuring the preconvulsive threshold by combining intermittent photic stimulation with a slow injection of metrazol. This provokes in normal subjects, for a quantity equivalent to about 10 mg. of the compound per kilo, a discharge of bisynchronous frontal spikes associated with muscular flexion jerks: the myoclonic response. Such a myoclonic threshold is normal in cases of organic lesions and in cortical epilepsy, while it is considerably lowered in those involving subcortical grey structures.

Among isolated procedures of physical activation, the most efficient is the intermittent photic stimulation method [Gastaut (8, 164, 208), Bickford (165a, 165b), and Ostow (166)]. It reveals the existence of a considerable number of cases of diencephalic epilepsy and provides a means of testing the integrity of the visual pathways [Gastaut (8)]. Besides this, it has been possible by this method to recognize a number of nonepileptogenic but irritative lesions of the diencephalon [Gastaut (8, 161, 167)]. Corriol & Gastaut (168) have used the electronic trigger circuit of Shipton & Walter to flash the stroboscopic lamp from one of the rhythms of the subject or from one isolated component of these rhythms.

Insulin has given good results in the hands of Baisset, Bugnard *et al.* (169) for the activation of epileptics while Hertz & Wulff (170) have used it unsuccessfully.

Schneider & Rémond (171) have attempted activation by intravenous morphine, Delay (12) and Verdeaux (173) by scopochloralose. Duplay (174) and Negrins (175) have described the activation of focal cerebral lesions by the effect of ventriculography which, like pneumoencephalography [Colombati & Pampiglione (176)], modifies the normal tracings. Greenblatt, Rinkel & Solomon (177) and Passouant & Latour (178) obtained interesting results by stimulation of the carotid sinus and the eyeballs to provoke EEG abnormality of vascular origin. Gastaut (179) observed some interesting facts with the intravenous injection of trimetadione in subjects showing bilateral synchronous discharges of subcortical origin. These disappeared during and after the injection, while discharges of purely cortical origin resisted the action of the drug much longer.

With regard to recording techniques, observations have been made on the use of auricular electrodes [McAvoy & Little (180)] which can, under certain conditions, be more active than the electrodes on the scalp [Gastaut (181)].

For this reason Stephenson & Gibbs (182) and Goldman (183) suggested indifferent electrodes outside the head or derived from Wilson's electrode.

Brazier (184, 185) has studied the distribution of electric fields on the head and tried in each case to demonstrate the orientation of the dipole generator. Fuster (186), Gastaut, Corriol, Naquet & Saint Jean (187, 188) claim a considerable advantage for the use of this method in daily work in order to evaluate without ambiguity the gradient of a potential difference due to a focus. As for the conventional method of recording from the surface with short interelectrode distances, it should be recalled that Bagghi & Basset (189) distinguish two types of phase-reversal: one true or "genuine," the other false or "instrumental." Offner opposes this view and believes that the two phenomena can be understood by a simple variation in the orientation of the dipole generator. Gastaut (181) and Gastaut & Paillas (190) drew attention to the interest of recording with large interelectrode distances and with the arrangement described as coronal triangulation for the exploration of the temporal regions. Roubicek & Hill (6), Faure *et al.* (192 to 195), McLean & Arellano (196) have found great advantage in the pharyngeal recording method. Gastaut (197, 198), Bickford (199), Spiegel *et al.* (201) and Hayne *et al.* (200, 202) have made recordings from subcortical regions in man.

The electrocorticographic technique was described by Jasper (8) and Walker (203). The French Society of EEG devoted its last scientific meeting to this subject (204).

Apart from the electrical activity of the brain proper, Kakegawa (205) has described a system for recording by an oscillograph the changes in cerebral blood flow, and Dawson *et al.* (206) have worked out a technique for the percutaneous recording of the action-potentials of man. This method may provide a considerable help in EEG experiments. Hunter & Jasper (207) have written about a method of cinematographic recording synchronized with the tracings and movements of the subject. Gastaut (208), by a different method of postsynchronization, has produced a sound-film in color on epilepsy provoked by flashes of light.

SPONTANEOUS ACTIVITY OF THE BRAIN

The origin and nature of cerebral waves have been the subject of several researches and even more numerous hypotheses, some of which have been vigorously defended by their authors. Bremer (209 to 213) considers that everyone is in agreement in ascribing the EEG to a fluctuation of electrical potential of the cortical grey matter [Bonnet (214)], but points out that there are three opposing theories to explain the rhythmicity of this fluctuation: cortical autorhythmicity, subcortical pacemaker, or the reverberatory action of the cortico-subcortical circuits. He considers that the first theory is the most tenable and the last, on the contrary, unfounded. This point of view is also expressed or supported by Margaria (215) and Moruzzi (216). Other authors hold a completely opposite view, as we shall see in dealing with thalamocortical relations.

Adrian (217) and Fessard (218) emphasize the importance of field effects on the generation and the maintenance of an autorhythmic focus. Walter (219) considers the question in an entirely different light in the 24th Maudsley Lecture; speaking from the ranks of the cyberneticians and reluctant to adopt the most facile solution "... for ambiguity seems the keynote of cerebral function," he puts forth once more the conception that the alpha rhythm is an example of a "scanning device." Brazier (220), Hoagland (221), and Gastaut (222) also have considered the application of cybernetic hypotheses to cerebral electrical activity. Prast (223) suggested that the alpha waves may be considered as the transient response of a transmission system with a narrow pass-band.

The characteristics of the spontaneous normal rhythms have been considered from the mathematical and physicomathematical point of view by Sato & Nakane (224), Imahori & Suhara (225), Wada & Kagekawa (226), Schaefer & Trautwein (227), while Rémy (228) has reviewed the analysis and synthesis of Walter.

Larsson, Melin & Ohrberg (229) have studied the variation of alpha frequency with age. Gastaut (181) described the normal activity of the temporal lobe and Masland, Austin & Grant (230) have shown that there is an "alpha temporal" component independent of all spread from the occipital alpha activity. Kennedy *et al.* (231, 232) defined the kappa rhythm which they have located in the same temporal region, but Ostow (233) did not differentiate it from the alpha rhythm of this region. Maddocks, Hodge & Rex (234) described an abnormal precentral alpha distribution. Gastaut (197, 198), and Hayne *et al.* (200, 202) have recorded from the white matter below the cortex rhythms which are only slightly different from those of the cortex itself, while Bickford (199) found an electrical inactivity. McCulloch (8) reported on the first results of phase analysis of spontaneous rhythm as obtained by his pupils (118, 119), while Darrow (235) studied the same phenomenon by another method. Greenstein & Strauss (236) described a slow activity in 38 per cent of normal subjects in auricular derivations. In the animal, Brookhart, Moruzzi & Snider (238) and Snider & Eldred (237) have studied the spontaneous activity of the cerebellum and Geets (239) those of the anterior brain of the frog. Garvin & Amador (240) have observed very carefully the electrical activity of the brain of an ape without finding any close correlation with cytoarchitectonics. In the case of individual cells, Renshaw & Rosenbaum (241) have shown that a lesion of the axon has no immediate effect on the excitability of the soma.

With regard to the borderline of the normal and the pathological, Stoller (242), Walter, Hill & Williams (243), Shafei (244), Cornil & Gastaut (245), Wada & Kagekawa (226) have dealt with various abnormal rhythms, their significance, and the manner in which they can best be interpreted. Aird *et al.* (246, 247) emphasize that a small amplitude asymmetry may often have a pathological significance.

The correlations between spontaneous rhythms and psychosomatic states have been described in a very general way by Pinelli (248), while

Saul & Davis (249), Wheeler & Koskoff (250), Bjerner (251), Kagekawa (252), Hess (253), and Ichinose (254) studied only those which concerned psychology and personality. Kennedy *et al.* (255, 256) relate the kappa rhythm to the phase just before the solution of problems. The relations between EEG and emotions have been particularly studied in man by Faure (257, 258), Rémy (259), Schiff *et al.* (260), Lhamon (261), and Miller & Lennox (262); they are described in animals by Wheatley *et al.* (264). Duensing (265) considered the relation between EEG and the state of consciousness and Mosovich (266) the modification of the EEG in the course of orgasm. Stafford-Clark & Taylor (267) found in murderers a proportion of EEG abnormalities, especially when the crime was committed without motive. Saul, Davis & Davis (263a) noticed a strict correlation between the psychological state of their patients submitted to psychoanalysis and their EEG. Liberson (263b) observed a relation between the proportion of alpha rhythm and the professional or psychological aptitude of a subject.

Jasper & Penfield (268) have made an interesting electrocorticographic study in man of the relation existing between voluntary movements and suppression of beta activity. Bates (269, 270) and Kibbler & Richter (271), on the other hand, found a close correlation between voluntary movements and the phase of alpha rhythm.

THALAMOCORTICAL RELATIONS

Hayne *et al.* (85, 202), Gastaut (197), Hécaen *et al.* (272), Meyers *et al.* (273), Williams & Parsons-Smith (274), Spiegel *et al.* (201, 275, 276) and Shinnars *et al.* (277) have compared in man, and Jasper (278), Gastaut & Hunter (279), and Spiegel (201) in animals the simultaneous spontaneous activity of the basal grey nuclei with that of the cortex. Most of these experiments, and particularly those made in man, have the serious defect of not recording simultaneously the interconnected regions of the two systems, the cortex and the thalamus being in fact two separate universes of which a great part of the regions are necessarily interdependent. In spite of this, and perhaps because of this, the general impression is that of thalamocortical "semi-independence" and Walker (280) insists on this view. This semi-independence is only compatible (a) with the total independence observed by Kristiansen & Courtois (281) when the cortex is perfectly isolated or by Wheatley, Knott & Ingram (282) when the hypothalamus has been injured, and (b) with the relative or absolute dependence which, on the other hand, has been noted in the numerous cases described by Lennox & Coolidge (283), Cress & Gibbs (284), Henriksen, Grossman & Merlis (285), and Darrow *et al.* (286) who observed that the sleep spindles and rapid rhythms of barbiturate drugs disappear after a lesion of the thalamus. Swank (287) relates barbiturate bursts to two corticothalamic neuronal circuits. Gastaut alone (161, 288) and with Hunter (279) has used intermittent photic stimulation combined with intravenous cardiazol to provoke irradiation of the electrical activity from the optic tracts first into the thalamus and later in the corresponding regions of the cortex. Jasper alone (278) and with Hunter (289,

290) and Moruzzi & Magoun (291) have confirmed Morrisson's observation that generalized response can be obtained on the cortex by the electrical stimulation of the reticular system of the thalamus. This response was not obtained, however, by Cohn (292) using strychnine stimulation, but was by Gellhorn (293, 294), who combined it with anoxia. Moruzzi & Lindsley, with Magoun (298, 299, 300), have shown how strictly the cortical electrical activity depends upon the integrity of the reticular activating-system which they have identified in the brainstem and the diencephalon. Chang (295) finally suggested that "the periodically recurring cortical waves following an afferent stimulus are the repetitive discharges of a reverberating cortico-thalamic-circuit"; an idea put forward sometime ago without convincing proof by Gastaut (197), but vigorously opposed by Bremer & Bonnet (296).

SUPPRESSION AND ACTIVATION OF CORTICAL ACTIVITY

Moruzzi *et al.* (297) consider that the waxing and waning of certain responses and the spontaneous bursts depend upon a periodical variation of basic excitability. Moruzzi & Magoun (298), Moruzzi (299) and Lindsley, Bowden & Magoun (300) have described the reticular activating-system of the brainstem and the diencephalon which, in the normal state, desynchronizes the electrical activity of the cortex and prevents sleep or unconsciousness. Lesions of this region, on the contrary, favor slow synchronization in sinusoidal bursts. Ward (301) has considered the same problem.

Work on suppression of cortical electrical activity has nearly all been directed to the study of the spreading depression of Leão. Whieldon & Harrevelde (302, 303, 304), Marshall *et al.* (305 to 309), Winokur *et al.* (310) have studied this problem emphasizing particularly the irritative and convulsive character which usually accompanies its effect when the stimuli are repeated. Sloan & Jasper (311) identified spreading depression with suppression induced by stimulation of suppressor areas. They considered the role which this phenomenon may play in the pathogenesis of focal epilepsy, and Echlin (312) that played in concussion. A special type of cortical inhibition appears during stimulation of the anterior cingulate gyrus. This phenomenon was described by Dunsmore *et al.* (313, 314), by Sloan & Jasper (311), and by Kaada *et al.* (315). It has also been observed in man by Penfield & Jasper (315) during stimulation at operation and by Jasper (8) and Gastaut (181) in the course of certain epileptic seizures deriving from a focus in that region. Dick, Bosma & Gellhorn (316) have noticed cortical suppression as an effect of afferent volleys, which seemed to place it in the type of general inhibition of the Richet type [Gerebtzoff (317)].

CORTICAL RESPONSE SECONDARY TO STIMULATION OF AFFERENT NEURONAL PATHWAYS

The form of the cortical response secondary to an afferent stimulus is complex, being composed of a rapid polyphasic component initially positive and of a slow element containing repetitive waves at alpha or even delta frequency. McCulloch (8, 318) relates the initial positive phase to the dis-

charge of neurones in the deep layers of the cortex and the negative phase which follows it to that of neurones in the more superficial layers. Bishop (319) admits on his part "that diphasic potentials indicate the firing of successive cell groups through synaptic passages; and that two groups of cells are oppositely oriented physically." Bishop identifies the slow component with the response of the mechanism responsible for the alpha rhythm. Gastaut (197) and Gastaut & Hunter (279), who share this point of view, try to identify this system with that of the diffused projection system of the thalamus, studied since the work of Moruzzi & Magoun (298) and Jasper (278). Chang (295) relates the slow response to a corticothalamic reverberating system. Gastaut & Hunter (279) find that the local application of metrazol increases only the rapid component, while the same drug on intravenous injection augments the whole complex and mainly the slow component, turning the pattern into that of the wave and spike; from this they infer that the system which produces the slow waves is not entirely included in the cortex but that it extends into the subcortical structures and that it must play a large part in the mechanism of epilepsy.

From a similar standpoint Gastaut, Albe-Fessard & Buser (320) have made a theoretical study of the form and polarity of epileptogenic cortical discharges. Gibbs & Hayne (321) proposed a very important law concerning the polarity of the cerebral responses: "when an electrical sign is referred to a relatively inactive area, negativity indicates local disturbance and positivity, distant disturbance." Bishop (322) has criticized this law from an experimental standpoint.

Responses evoked by a specific stimulation of a peripheral pathway have been worked on by Jarcho (323), Marshall (324), Forbes *et al.* (325), and Gastaut & Hunter (326). They studied the cortical excitability of the cortical afferent systems. The data should be valuable in estimating the refractory period of the cortex and sufficiently regular results have been obtained to suggest a possible explanation of the frequency of slow hypersynchronized waves in the cortex.

The response of the optic afferent system in its form and its time-relation has been given the greatest attention by Chang & Kaada (327), Bickford (328), Noell & Chinn (329), Buser (330), Gastaut (197), Monnier (331, 332), and Cobb (333). The response to repeated flashes has also been investigated by Morin, Gastaut & Corriol (334), Rémond & Thiry (335), Thiry (336), Bickford (337) and above all by Walter & Walter (338) in a remarkable study. Buser & Ecoiffier (339) and Fessard & Buser (340) have made an analytical study of this response in the rabbit. Fields, King & O'Leary (341) have experimented on the response of the occipital cortex to repeated direct stimulation of the lateral geniculate body. The response of the auditory specific system has been studied by Bremer & Bonnet (342), Neff & Yella (343), Thurlow & Gross (344), Lipman (345) and Gastaut & Corriol (346). The response of the proprioceptive afferent system has been worked on by Gay & Gellhorn (347).

The response evoked by stimulation of a nonspecific pathway differs

little, either in form or in polarity, from the phenomenon above described [McCulloch (8, 318), Woodbury (348)]. Its topography depends upon the neuronic connections of the stimulated point; it is this property which is the basis of the technique known as "physiological neuronography," used extensively for the study of corticocortical connections as well as subcortical ones. The preferred stimulus is usually local application of strychnine or of another convulsive drug. Some workers, however, prefer electrical stimulation and others, for chronic studies, the use of aluminum oxide cream. Using these methods, McCulloch studied the connections of the frontal lobes (349), Sugar *et al.* (350 to 353) those of the cortical regions buried deep in the sulci, Petr, Holden & Jirout (354) those of the tip and of the surface of the temporal lobe, and Marsan, Stoll & Jasper (355) those of the temporal tip only; Pribram, Lennox & Dunsmore (356) studied those of the orbitofrontotemporal limbic region and of the hippocampus. Woolsey & Chang (172) have produced a retrograde response of the cortex by stimulating the pyramidal tract. Ades & Brookhart (357) and Galambos & Rosenbluth (358) have investigated the auditory pathways in the central regions, while Berry, Karl & Hinsey (359) have followed the spinothalamic tract and the medial lemniscus as far as the thalamus, and Mountcastle & Henneman (360) have established the somatotopic arrangement of the touch region in the thalamus of the cat. Snider & Eldred (361) and Hampson (362) have studied the specific corticocerebellar sensory connections showing quite definitely the inadequacy of the conception of a purely proprioceptor cerebellum. Schoepfle (363) has traced the olivocerebellar connections. Kopeloff *et al.* (364) and Sawa (365) observed that the section of the corpus callosum suppressed the transmission between hemispheres of both the alumina and the strychnine spikes. In quite a different aspect of such work, Popov (366, 367) studied in the rabbit the EEG during the formation of cortical conditioned reflexes.

CHANGES IN CEREBRAL ELECTRICAL ACTIVITY PRODUCED BY PHYSICAL OR CHEMICAL STIMULI

The stimulation of cerebral grey matter, even when localized and limited, invariably produces, whatever its nature, a local activity, which tends to be propagated in one of the two manners described by McCulloch (318): (a) a propagation which tends to be centrifugal and moves very slowly from the excited point within the cortical feltwork, a propagation which is carried on through numerous synapses with a speed of about 10 mm per sec.; (b) a propagation tending to follow the course of the projection axons leaving the stimulated regions and having a great velocity towards the predestined points which of course are always the same. Dow (368) has made a very careful study of this fact after the stimulation of a cerebellar folium. The slow propagation, which is both local and multisynaptic, takes a number of forms, which according to Whieldon & Harreveld are: (a) an after-discharge, (b) a spreading depression, (c) high frequency low voltage activity, and (d) convulsoid activity. The rapid transmission to a distance has the effect of a

bombardment of high frequency of neuron groups connected with the end of the pathways; this secondary discharge in its turn may be propagated in any of the two ways just described. Changes in the intensity and duration of the stimulus affect principally the after-discharge and the transmission at a distance, while the repetition of a stimulus at intervals of about ten minutes increases the low voltage fast activity and the convulsoid activity. Walker & Johnson (369) distinguished two types of after-discharges, one normal and one pathological, and induced both types during neurosurgical operation in order to assess the state of the cortex.

Changes induced by physical stimuli.—Among the changes induced by physical stimuli, the most frequently studied are those produced by electricity and surgical operations, for these form the basis of the electroconvulsive therapy and psychosurgery both of which are so widely used now.

Electroshock can be made to produce quite local changes. For example, Clark & Ward (370, 371) and Johnson *et al.* (372) used it to produce a purely cerebellar seizure. Most of the works, however, have dealt with general changes of the EEG produced by electroshock or similar procedures. Lorimer, Segal & Stein (373) and Hayes & Park (374) studied the current path in the electroshock. The study of the seizure itself has been made by Meyer-Mickeleit (375), Bickford & Rome (376) and Gastaut *et al.* (377). Bickford has made the curious observation that in delayed seizures the EEG can remain normal for several minutes after the shock. Jung (378) has devoted an extremely interesting experimental study to the electrically-induced seizure recording simultaneously from many subcortical structures. It is, of course, the study of recordings following one electroshock or a series of electroshocks and the comparison of these records with those obtained before treatment that has occupied most of the workers (379 to 387). Electrocortical was the subject of many studies (388 to 396).

Psychosurgical operations have provided opportunities for corticographic recordings and corticosubcortical stimulations, which have already been described. Various workers (283, 286, 397 to 404) have studied the EEG before and after prefrontal lobotomy and have attempted to work out some relations with the evolution of the disease. The EEG in transorbital lobotomy and undercutting has been studied by Henry (403), while the selective partial ablation has been examined by Kershman & Vasquez (405) and Zingarelli (406).

Included among physical stimuli should be mentioned also the studies of Teschan & Gellhorn (407) and Ten Cate *et al.* (408) on the effect of changes of local or general temperature on the EEG. The former has very little effect while the second has a considerable action.

Changes provoked by chemical stimuli.—Hoagland (409, 410) has studied the correlation between cerebral metabolism and certain characteristics of the EEG. Darrow (411) described the relations between this metabolism and the electrical convulsive activity. Faure (412) has studied the effect of drugs on the activity of the base of the brain. Toman & Davis (413) have written an excellent general review of 67 pages and 350 references on the effect of drugs upon the electrical activity of the brain.

Among the drugs with a cerebral depressant action, Swank *et al.* (414, 415), Tucci *et al.* (416) and Alexander *et al.* (417) have studied the action of barbiturates and Faulconer *et al.* (418, 419) that of nitrous oxide. Anti-epileptic drugs, though intensely studied from a therapeutic standpoint, have not received very much attention in relation to their effects on the EEG. Lennox (420) and Toman (421) have made a general study of them. Little & MacAvoy (422) reported an acceleration of the rhythms under the effect of mesantoin, and Gastaut (179) has studied the effect of trimethadione injected intravenously on certain epileptic discharges. In the group of drugs with a stimulating cerebral action, strychnine has only been investigated in relation to the theoretical studies reported elsewhere. Johnson *et al.* (423) noted, however, that in the cerebellum it produces rhythms of 10 to 30 c.p.s. instead of focal strychnine spikes. The action of cardiazol has been studied by Bertrand *et al.* (424), Kagekawa *et al.* (425), Gastaut *et al.* (426). The convulsive action of agen (nitrogen trichloride), which is used to bleach flour, was studied from an EEG point of view by Silver, Monahan, Klein & Pollock (427, 428, 429), and by Newell *et al.* (430). Pollock & Bain (431) reported that beta-chlorinated amines like DDT can produce fits starting in the cerebellum. Marsan, Fuortes & Marossero (432) have shown that ammonium chloride does not act directly on the cortex, but through the intermediary of circulatory changes. Amphetamine can produce unilateral convulsions starting in foci which are otherwise quiescent (433).

Of the autonomic mimetic compounds the one which has been the most studied is acetylcholine. Barnes & Beutner (434 to 438), from the observations of their models and from theoretical considerations, continued to emphasize what they called the cholinergic origin of the brain waves. Even the slow waves of hyperpnea may be explained, according to them, by a mechanism of the same order (439), an opinion partially confirmed by Darrow (440) who found that the maintenance of the level of acetylcholine during hyperpnea prevented the appearance of these slow waves. Bremer & Chatonnet (441) have obtained cortical stimulation by intravenous injection of very weak doses of acetylcholine while Hyde *et al.* (442) and Marrazzi & Hart (443) found that the local application of this drug greatly facilitated the convulsive response of the cortex. Although these facts have been known for sometime, some doubts have been cast upon them by Marsan & Fuortes (444), who have observed a flattening of the records during convulsions induced by intravenous injections of acetylcholine and by Case & Funderburk (445), who deduced from the action of atropine on cortical activity that acetylcholine is not necessary to the mechanism of convulsive discharge. Nearly all the authors who have studied the effect upon the EEG of anticholinesterases such as physostigmine or prostigmine, found that these compounds had almost the same effect on the cerebral cortex as acetylcholine itself [Hyde *et al.* (442), Bremer & Chatonnet (441), Brooks, Ransmeier & Gérard (446)]. Only diisopropylfluorophosphate has given contradictory results; Hyde *et al.* (442) and Kelen & McEachern (447) did not find a convulsant effect nor even a very clear action of any kind on the EEG, while Rowntree & Nevin (448) have reported a flattening of the records with the

appearance of slow waves. Hampson *et al.* (449) on the contrary confirmed the highly convulsive property described principally by Freedman *et al.* (450, 451), observing moreover that the changes in the EEG were proportional to the decrease of activity of cerebral cholinesterase. Cohn, Tower & McEachern (452 to 456) have established very interesting relations between the level of acetylcholine and cholinesterase in the spinal cord and the clinical and electrical state of patients with a history of head-injury, electroshock therapy or epilepsy. They found relations very close to those obtained by Bernstein in the animal and notably that the higher the level of acetylcholine and the smaller the level of cholinesterase, the more marked are the clinical signs and the flatter are the tracings.

With regard to curariform compounds, they do not appear to have any effect upon the EEG either with therapeutic doses (457, 458) or with very much higher doses. Ostow & Garcia (459) have observed the disappearance of evoked, then of spontaneous activity, these findings permitting the inference of a blocking of synaptic conduction. Kaada (460), using myanesin, observed this blocking only for the complex multisynaptic pathways. The latter drug has also been studied by Gammon & Churchill (461) and Last & Weil-Malherbe (462). The latter observed in the rabbit some effects which they attributed to a direct action on subcortical structures. Spiegel & Wycis (463) confirmed this point of view in man and even go so far as to localize the effect of myanesin at the level of the hypothalamus.

Churchill & Gammon (464) and Esmond *et al.* (465) studied the action of antihistamine compounds of a synthetic nature, particularly dramamine, which, according to the latter authors, would be convulsive in high doses and anticonvulsive in weak doses. Oddly enough, epinephrine has been studied very little (466).

Of metabolic agents whose effects on the EEG have been the most studied are anoxia or carbon dioxide. General reviews have been written on the cerebral changes produced by anoxia (468, 469) and on anoxic convulsions (467, 468, 469). Gellhorn (469) comes to the conclusion that anoxia and asphyxia inhibit the cortical functions by freeing those of the hypothalamus, explaining in this way that a cortical seizure can be prevented by this method whereas generalized seizures would be facilitated. Prast & Noell (126 to 129, 470 to 474) have noticed that the first manifestations of anoxia are waves of 5 to 7 c.p.s. which appear before the first psychic changes and they have shown them by a special method of analysis. Noell & Chinn (475, 476, 477) have studied the effect of anoxia on the occipital response to a slow flicker and used the time taken for complete suppression of the evoked potentials to establish a "cortical survival-time" which is of the order of 65 sec. in the rabbit. Before the depressive effect of anoxia and in the course of the phase of recovery which is associated with readmission of oxygen there is a brief supranormal phase of excitability (478). Gellhorn & Heymans (479) confirmed by means of a different technique the existence of a supranormal phase of recovery. Lipton & Gibbs (480) studied in man the effects

on EEG produced by anoxia resulting from an injection of sodium cyanide. Van Harreveld (483) has found during asphyxia a depolarisation of neurones revealed by continuous negative polarity of the grey substance.

In the same category are the observations of Goldensohn *et al.* (481) on the so-called "diffusion-respiration" during which there appears to be an electric silence lasting 20 min. followed by a progressive recovery after the end of the experiment. Millar (482) has observed abnormal coma rhythms in a surgical patient after a cardiac arrest of 40 min.

The effects of carbon dioxide used therapeutically for narcosis described by Baudouin, Rémond & Delarue (484) have been the subject of intensive study on the part of Pollock, Silver *et al.* (485 to 490) who claim to be able to distinguish two types of convulsive attacks: (a) those provoked by electroshock, metrazol, strychnine, and insulin which are inhibited by carbon dioxide; (b) those produced by nitrogen mustard, agensised protein, DDT, and hyperoxia which are facilitated by carbon dioxide, the former of these seizures beginning in the cerebral hemisphere and the latter in the cerebellum.

Convulsions produced by fluoroacetate were studied by Kelen & McEachern (447) and those produced by insulin by Weinland (491). Jordan *et al.* (492) found that adenosinetriphosphate behaves as an anti-convulsant. Gozzano *et al.* (493, 494) have studied the effects of vitamin B and Hoeffler & Glaser (495) devoted an important chapter of their work to the action on the EEG of adrenocorticotrophic hormone (ACTH). Various chemical agents have been studied in relation to the EEG; potassium chloride (496), parpanit (497), quinine salts (498), and pervitine (499).

According to Aird (500), certain dysrhythmias may be the result of an augmentation of the permeability of the blood-brain-barrier. Gozzano & Colombati (501) and Cazzullo & Pacella (502) have studied the effects of anaphylactic shock and cerebral allergic lesions on the EEG. They found local or more generalized convulsive effects, according to the mode of production of the reaction itself. Ectors & Ashlogh (503) have studied the local convulsive action of antibiotics.

Changes produced by physical and chemical stimuli.—Gellhorn *et al.* (504, 505) observed that exteroceptive stimuli produced increased response in the specific cortical area under the effect of progressive poisoning by picrotoxin; these responses became finally repetitive and irradiated to non-specific areas and to the hypothalamus when the poisoning level was sufficiently high. These authors also reported that afferent proprioceptive impulses increased the tendency to convulsive discharge of the cortex. Noell (477) has observed a similar intensification and irradiation of the responses to flashes of lights during the supranormal initial phase of anoxia. Gastaut (5, 8, 161, 162, 163) has studied particularly the phenomenon in man and in animals (279); he considers the irradiated response as the elementary unit in the general convulsive attack, whether spontaneous or induced, and showed that it is initiated by a discharge in the thalamus. He suggested a

therapeutic procedure of convulsive nature adaptable to psychotic patients based on the combined action of metrazol and flicker. This he has called "photo-shock" and it has already given satisfactory results (506, 507, 508).

GENETICS AND DEVELOPMENT

The study of EEG in twins has always attracted considerable attention (509, 510) as has also the hereditary character of the EEG (511, 512). The development of the EEG in the foetus of the guinea pig has been studied by Gallant, Tyler & Flexner (513) who observed the first appearance of cortical rhythmicity at the moment when, as far as can be told by morphological criteria, the neuronoblast becomes neuronocyte, i.e., about the 46th day of intrauterine life. Snider & Jacobs (514) have reported on the ontogenetic development of the spontaneous rapid activity in the cerebellum. Gibbs & Knott (515) made the analytical study of the EEG component in relation to age. Sureau, Fischgold & Capdevielle (516), Hughes *et al.* (517, 518), and Ellingson & Lindsley (519) studied the EEG of the newborn, and Cornil & Corriol (520) and Lennox *et al.* (521) that of small and older children. Shinnars, Hamby & Krauss (277) and André-Thomas & Fischgold (522) have recorded respectively electrocorticogram and EEG in an anencephalic idiot

EEG AND SLEEP

The normal rhythms of spontaneous sleep have been studied by many authors, among whom are Gibbs (523), Liberson (524), Hess (525), and Rubino (526). Monnier (527) has studied the same phenomena in the cat in sleep produced by stimulation of the hypnogenic center.

Knott, Hayne & Meyers (528), recording directly from the thalamus and the corpus striatum in sleeping subjects, and Faure (529) with the help of a simple pharyngeal electrode, have reported the first appearance of the early signs of sleep in the formation at the base of the brain. Lennox & Coolidge (283), Cress & Gibbs (284), Henriksen *et al.* (285) and Darrow & Henry (286) also have demonstrated the thalamic nature of sleep spindles. Brazier (530) studied the electrical field on the surface of the head during sleep and demonstrated the usual cortical participation during movements which occur in the course of normal sleep (531). Bjerner (532) studied the EEG of subjects deprived of sleep during a long period. The EEG of hypnosis was studied by Barker & Burgwin (533, 534) Ford & Yeagu (535) and Planques, Baisset & Grèzes-Rueff (536).

Inevitably condensed and abbreviated, this review contains no mention of any clinical observation whatsoever. Particularly to be regretted is the absence of any mention of the works on epilepsy and cerebral tumors which alone would make up half of the total volume of the publication on EEG during the last two years. Nevertheless, it was felt better not to sacrifice the physiological survey, which is the main purpose of this work, to a list of clinical observations which would better appear in more specialized reviews.

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METABOLIC FUNCTIONS OF THE ENDOCRINE GLANDS¹

BY JANE A. RUSSELL²

*Department of Physiological Chemistry, Yale University School
of Medicine, New Haven, Connecticut*

As in the past several years, it has been impossible to mention here all the papers appearing in the period of review which might have been included under the title of this chapter. Emphasis has been placed on the metabolic functions of the hormones with evidence bearing on the physiology of the endocrine glands as such included only in certain instances. With few exceptions, no discussion has been attempted of papers which have been available to the author only in abstract form.

THE HYPOPHYSIS

Activation of the adenohypophysis.—It has become apparent that most of the anterior lobe hormones, like those of the neurohypophysis, are secreted not at constant rates, but that the functioning of the gland must be controlled in such a way that the trophic hormones are released at rates varying with the physiological state and needs of the animal. The nature of the mechanisms which may excite secretion by the adenohypophysis is now under active investigation (1, 2). Green & Harris suggested earlier that local neuro-humoral stimulation of the gland might occur via pathways from hypothalamic areas and the hypophyseal-portal blood vessels. These authors have now confirmed by direct observation in the living rat the direction of flow of blood in these vessels as from the median eminence toward and into the pars distalis (3). Harris has further pointed out that after stalk section, regeneration of the portal vessels may occur readily (4, 5). Unless measures are taken to prevent this, as by insertion of a plate of some sort, severing the direct neural pathways from the hypothalamus to the pituitary would not necessarily interrupt permanently the vascular connections. In stalk-sectioned rats, Cheng *et al.* (6) observed maximal reduction in the adrenal ascorbic acid after injection of histamine. Later, they reported submaximal stimulation of the adrenal by histamine in hypophysectomized rats bearing intra-ocular grafts of anterior lobe tissue (7). Fortier & Selye (8), using cold as a stimulus, reported identical changes in adrenal ascorbic acid in normal or stalk-sectioned rats and in hypophysectomized animals with intra-ocular grafts. It would appear that in the rat, at least, neither neural nor vascular connections with the hypothalamus are required for increased secretion of adrenocorticotrophic hormone (ACTH) following stress.

¹ This review covers approximately the period from June, 1949 to July, 1950.

² Present address, Department of Biochemistry, Emory University, Georgia.

The nature of the stimulus to the pituitary is still in question. A direct action of epinephrine on the secretion of ACTH by pituitary tissue was seen by McDermott *et al.* (9); the blood eosinophil count was shown to fall following the instillation of small amounts (0.2 μ g.) of epinephrine into the eye of a hypophysectomized rat bearing an intra-ocular graft of pituitary tissue. Recant *et al.* (222) reported that epinephrine induced eosinopenic responses in the dog in which neural and vascular connections between the hypothalamus and pituitary were severed, but also that formaldehyde injections induced responses in completely sympathectomized dogs. On the basis of change rates in blood eosinophil counts following various stimuli in cord-sectioned or adrenodemedullated rats, Long *et al.* (10, 10a) propose a biphasic system: initial stimulation of the pituitary by epinephrine released following sympathetic excitation, and a slower phase of activation not requiring the mediation of nervous activity (possibly acting through the level of circulating cortical steroids).

Growth and nitrogen metabolism.—The recent availability of purified growth hormone in relatively large quantity has allowed the confirmation and extension of a number of observations made previously with crude anterior pituitary extracts or growth hormone concentrates. Li & Evans (11) have summarized such data on changes in nitrogen balance, plasma phosphate and phosphatases, and body composition. Greenspan *et al.* (12) have described the bioassay procedure for growth hormone in which the width of the tibial epiphyseal cartilage is measured in hypophysectomized rats. The useful range of dosage, given over a period of four days, is 5 to 100 μ g. per animal. No difference in response was seen whether the hormone was given once or twice a day, or given by subcutaneous, intraperitoneal, or intravenous route. Greenbaum & Young noted that the increase in mass of various tissues of the growth hormone treated rats was not uniform. No apparent reasons for differing responses of several muscles could be described (13). Diminution in the plasma glutamine level was seen in dogs given a single large dose of growth hormone (14).

Requirements for pantothenic acid appear to be increased during growth hormone action in rats (15). High mortality among hypophysectomized rats fed a commercial laboratory diet, but survival and growth when the animals were fed purified complete diets, were reported by Shaw & Greep (16). Other investigators, including the present writer, have had no difficulty in maintaining hypophysectomized rats on ordinary diets which were adequate for normal animals. Some continued growth of rats hypophysectomized at an early age has been usual [see also (335)].

In nephrectomized rats in which the blood urea changes were used as a measure of amino acid metabolism, growth hormone³ given acutely appeared to have no effect on the basal rate of protein catabolism; but when an amino

³ A partially purified preparation was used; the results have since been duplicated with highly purified growth hormone (Russell, unpublished).

acid mixture was given intravenously, the rate of urea production in the following hour was much lower in the treated than in control animals (17). Since the rate of removal of amino nitrogen from the blood was not diminished but enhanced somewhat, it appeared that in these circumstances growth hormone was affecting the anabolism of the administered amino acids rather than the catabolism of body protein. A similar interpretation is afforded by the data of Hoberman (195) on the disposition of isotopic glycine in fasting rats (see under ADRENAL CORTEX page 345). Here growth hormone did not affect the catabolism of body protein but tended to increase synthesis. It is possible that more pronounced effects on synthesis might have been seen in fed animals.

The relationship of insulin to the action of growth hormone on nitrogen metabolism is still unclear. In depancreatized cats on constant insulin dosage, growth hormone induced significant nitrogen retention but less than was seen in normal cats (18). Hypophysectomized rats treated with alloxan and then given growth hormone were reported to grow as well as control animals not given alloxan [but in these circumstances no evidence could be provided as to the state of the pancreas in the treated animals (19)]. Depression of the blood amino nitrogen was observed in alloxan diabetic rats (20) and in depancreatized cats given growth hormone (18). However, van Wieringen & de Jongh (19, 21, 22) reported that while large doses of growth hormone (partially purified) would diminish the extent of the increase in blood amino nitrogen in eviscerate decapitate rats, this was not seen in rats previously made diabetic with alloxan. It may be pointed out in this connection that diminution of the blood amino nitrogen, particularly in animals with functioning livers, may not be related quantitatively to the degree of nitrogen retention in the tissues. From the data available at present, it seems that some nitrogen retention may take place when growth hormone is given in the absence or near absence of insulin but that insulin may be necessary, possibly in increased amount, for maximal or prolonged retention of nitrogen. An interesting new observation in connection with the synthesis of tissue is that of Cotes *et al.* (23) who found that purified growth hormone was a highly active galactopoetic agent in the cow in the declining phases of lactation.

Gaebler and his colleagues have studied effects of growth hormone on the content of various enzymes in tissues (24, 25, 26). The alkaline phosphatase of the tibia was found to be low after hypophysectomy and to be greatly increased following growth hormone treatment (24). In kidney, the alkaline phosphatase was found diminished after hypophysectomy but that of liver was found to be increased; growth hormone restored the renal enzyme and partially affected that in the liver. No changes were seen in the acid phosphatases of these tissues (25). Liver and kidney D-amino acid oxidase or muscle succindehydrogenase concentrations were not affected in normal or hypophysectomized rats given growth hormone. A reduction in the amount of D-amino oxidase in untreated hypophysectomized animals may

have been the result of thyroid atrophy (26). Cagan *et al.* (27) reported increased quantities of L-amino acid oxidase in livers of hypophysectomized rats.

Moon *et al.* (28) note a high incidence of hyperplasia of peribronchial tissue and of lymphosarcoma of the lungs of rats after long-continued administration of growth hormone. This paper appears to be the first of a series reporting pathological changes in such animals. In more acute experiments, Schulman & Greenberg (29) observed no differences in the growth of tumor transplants in mice treated with the hormone.

Although the action of administered growth hormone has been demonstrated in a variety of species of animals, convincing evidence of its effects in man has not yet been obtained. Bennett *et al.* (30) and Lewis *et al.* (31) could demonstrate no action of purified growth hormone on nitrogen balance in two patients with idiopathic dwarfism and in one who was a cretin being treated with thyroid hormone. These experiences are in general agreement with unpublished observations of other investigators. It would be of interest to find whether concomitant administration of insulin would allow some degree of nitrogen retention in man or if growth hormone from other species than cattle would be effective.

Sheehan *et al.* (32, 33), in an excellent summary of the effects of proved hypopituitarism in man, point out that emaciation, cachexia, or progeria is seldom seen if the nutritional status has been adequate. Even when damage to the pituitary has been most severe survival may be prolonged for many years. In these respects, as in others, hypopituitarism in man resembles the condition as seen in most other species. A possible role of the growth hormone in the maintenance of normal kidney function is indicated by the work of White *et al.* (34, 35).

Metabolism of carbohydrate and fat in vivo.—It now appears that highly purified growth hormone may have diabetogenic properties and that the content of this hormone in crude pituitary extracts may account for a substantial part of the effects of the latter on carbohydrate and fat metabolism. Milman & Russell (20, 36) have found in acute experiments that purified growth hormone lowers the blood glucose in normal fasting rats, but that in animals previously treated with alloxan, whether mildly or severely diabetic, the blood sugar was elevated after growth hormone. The suggestion from this data would be that growth hormone normally calls forth increased secretion of insulin, but that when this is not possible, hyperglycemic effects are seen. In fasting normal or hypophysectomized rats given growth hormone, the rate of disappearance of tissue glycogen was diminished (37, 38), and in normal rats fed glucose, the storage of glycogen was increased and the R. Q. depressed (20, 38). For the effect to be seen in fed animals, the presence of some adrenocortical hormone was required (38). Sensitivity to exogenous insulin was reduced in normal rats (20, 36) and in hypophysectomized (39) dogs treated several hours beforehand with growth hormone. The net impression of these observations is that the effect of growth hormone, in opposi-

tion to that of insulin, is to diminish the utilization of carbohydrate either oxidatively or via formation of fat.

In more prolonged experiments with growth hormone (i.e., over several days), Cotes (40), Campbell (41), and their co-workers have induced temporary glycosuria in normal cats and dogs, and Houssay & Anderson (42) have reported the production of sustained hyperglycemia in cats and dogs (partially depancreatized) and in normal frogs and toads. In the fractionation of ox pituitary extracts, growth promoting activity in rats and diabetogenic activity in cats appeared to remain parallel (43). ACTH given to cats and dogs was relatively ineffective (41, 42). In rats which were mildly diabetic after alloxan treatment, Gaarenstrom *et al.* (44) observed that a partially purified growth hormone preparation tended to increase the amount of glucose excreted, and the present author has confirmed this observation with highly purified growth hormone (unpublished). In this type of experiment, the rat appears to be relatively resistant to the diabetogenic action of growth hormone, but to be more susceptible to the action of ACTH than is the cat or dog.

Gaarenstrom *et al.* (45) have reported that in hypophysectomized rats given large quantities of glucose, the blood sugar one hour after the last glucose dosage was elevated much above normal and that prior chronic treatment with growth hormone tended to reduce the blood glucose level in these conditions. Since many of the untreated animals died, it seems possible that the apparent increase in glucose tolerance could have been the result of improvement in the general condition of the animals following growth hormone treatment.

In view of the apparent effect of growth hormone in depressing carbohydrate utilization, one might also expect the hormone to increase the mobilization and catabolism of fat. Li *et al.* (46), using fasted normal rats, observed small but significant increases in liver fat content after both growth hormone and ACTH. Fasting normal mice were found by Weil & Ross (47) to be more sensitive to this action than rats, the liver fat being doubled seven hours after the administration of 0.5 mg. per 100 gm. of growth hormone. Payne (48), obtaining variable effects of different pituitary extracts on liver fat of rats, could not attribute the activity to any known principle. None of the fractions employed here was active in adrenalectomized rats, but if cortical extract (itself ineffective) were given, the usual increases in liver fat were obtained. No relationship between fat mobilization and thyrotrophic activity of pituitary extracts were seen (49). Ennor (50) observed increased fat in the livers of guinea pigs treated with crude extracts of ox pituitaries and when slices of the livers were incubated *in vitro* increased production of acetoacetate.

Although the reports outlined above suggest that most of the metabolic activity of pituitary extracts may be attributable to the content of growth and adrenotrophic hormones, it cannot yet be said with certainty that this is entirely the case, for the criteria for purity of protein hormones are not

absolute nor have appropriate bioassay procedures been shown to yield quantitative recoveries of activities from whole extracts.

Experiments in vitro.—Recent attempts to demonstrate the action of anterior pituitary factors on the metabolism of tissues *in vitro* have been confined to experiments with the isolated rat diaphragm. Villee & Hastings (51), observing the metabolism of C^{14} -labeled glucose by isolated diaphragm tissue, confirmed earlier reports that the rate of metabolism of glucose was enhanced in tissues taken from hypophysectomized rats. Glucose uptake, carbon dioxide production, and glycogen formation were all above normal, whether insulin was added to the medium or not. Park & Krahl (52) have made the further observation that the injection of anterior pituitary extracts into normal or hypophysectomized rats 3 to 24 hours before experiment reduced the rate of glucose uptake by the diaphragm. The activity appeared to accompany the growth hormone during fractionation, and very small doses of highly purified growth hormone were later shown to be effective in hypophysectomized rats (53). The pituitary factor was said to be without action in hypophysectomized-adrenalectomized animals, but the concurrent administration of cortical extract (itself ineffective) allowed the inhibition of glucose uptake by growth hormone in these animals. The enhancement of glucose uptake by insulin added *in vitro* was unaffected by hypophysectomy or by the administration of pituitary factors. On the other hand, Li *et al.* (54) observed no differences from the normal in the uptake of glucose or formation of glycogen in the diaphragms of hypophysectomized rats. Although growth hormone (or ACTH) given 24 hours before experiment had no effect alone, they did appear to inhibit the action of added insulin. In the work of Stadie *et al.* (104) on the combination of insulin with diaphragm tissue (see further under INSULIN), growth hormone given to the animal before experiment also prevented the insulin effect on glycogen formation.

These observations *in vitro* are in general confirmatory of earlier indications from work *in vivo* as to the enhancement of rates of carbohydrate utilization in the absence of the pituitary and of opposition between the actions of pituitary factors (growth hormone?) and of insulin. The precise point at which the metabolism of carbohydrate is affected by the hormones is not clear. Since in many of the *in vitro* experiments, glucose uptake from the medium and glycogen formation have run approximately in parallel, it has been inferred that the hexokinase reaction⁴ was involved. In experiments *in vivo*, however, glycogen deposition or maintenance has been increased by pituitary (and adrenal) factors at the same time that the catabolism of carbohydrate appears to have been reduced, indicating an interference in the later stages of carbohydrate metabolism. The experimental conditions used *in vitro* have not been such as to allow a demonstration of effects of the hormones, if there are such, on the metabolism of preformed glycogen.

⁴ The first stage of glucose metabolism, phosphorylation by adenosinetriphosphate (ATP).

Neurohypophysis.—Ames, Moore & Van Dyke (55) and Taylor & Noble (56) have reported further observations on the appearance of antidiuretic substances in the urine in conditions of relative dehydration. A similar substance was found in the urine of human subjects after fainting and after electroshock treatments, but not in hemorrhage without fainting, in blackout, nor in eclampsia (56). Antidiuretic hormone (ADH) was detected also in jugular vein blood but not in the femoral vein after the injection of hypertonic salt solutions (55). Stevenson (57) has reported low water intake and delayed water excretion in rats with hypothalamic lesions known to produce obesity; he has suggested that chronic dehydration resulting from disturbed regulation of water intake could lead to increased secretion of ADH and perhaps also to other deficiencies in kidney function noted in these animals. Both ADH and oxytocic factors were found in much smaller quantity in the pituitary glands of new-born than in those of adult human beings (58). The very dilute urine of new-born infants may be in part explained as due to low production of ADH and perhaps in part to relative insensitivity of the kidney to the hormone.

The observations of Stewart (59) indicated that mammalian posterior lobe extracts greatly accelerated the uptake of water through the skin of frogs placed in hypertonic media, but did not affect the more rapid rate of water loss into hypertonic surroundings. Pressor but not oxytocic extracts of posterior lobe tissue were observed to decrease the tolerance to glucose in eviscerated rats given insulin (60). On the other hand, Fraser (61) reported that concentrated pressor extracts had much less hyperglycemic activity in dogs than did oxytocic extracts, while plasma phosphate was decreased by oxytocic but increased by pressor fractions.

The preparation and properties of highly purified and concentrated oxytocic hormone have been described by du Vigneaud and collaborators (62, 63).

INSULIN AND EXPERIMENTAL DIABETES

Metabolism in diabetes and the role of insulin.—The production of experimental diabetes in two additional species has been reported. In the calf (64), either pancreatectomy or alloxan administration induced a state characterized by mild postprandial hyperglycemia, reduced glucose tolerance, and normal or low blood glucose levels on fasting. Renal damage was severe after alloxan. Mice exhibited severe and lasting glycosuria after operative removal of most of the pancreas (65). Attempts to produce permanent diabetes in the guinea pig by alloxan administration have not been successful; hyperglycemia when present lasted only a few days, and toxic effects of alloxan were frequent (66, 67). Greenfield & Sanders have summarized available data on the effects of complete pancreatectomy in man (68). These authors indicate that if the nutritional status of the patient is good, the requirement for insulin does not appear to differ from that common in clinical diabetes mellitus. Allen & Lisa (69) report in detail on the survival for 12

years of a dog having severe diabetes following near-total pancreatectomy. Haist (70) and Himsworth (71) have presented excellent reviews of the factors affecting pancreatic function.

Three different groups of investigators have reported that the liver glycogen content in patients with diabetes mellitus (untreated with insulin for several days) may be within the normal range. Specimens were obtained by biopsy and analyzed chemically (72) or photometrically after staining (73), or judged by histological methods (74). Although the glycogen values tended to be lowest in patients with severe ketosis, there was not always any evident relationship to this factor. It has long been supposed that liver glycogen is absent if insulin is not available, but in fact, critical observations made in diabetic animals are not to be found in the earlier literature. Fasting, alloxan-diabetic rats tend to have more glycogen in the liver than normal animals, as has been reported several times, and completely depancreatized cats may have normal liver glycogen values even in the presence of severe acidosis (75). Insulin given with glucose may tend to increase the rate of deposition of liver glycogen as it does muscle glycogen, but the quantity of insulin available does not appear to be critical in determining the presence or absence of glycogen in the liver.

Somogyi (76, 77) has presented evidence to the effect that insulin given with glucose to normal men increases the arteriovenous difference seen at a given arterial glucose level. When glucose was not given, a small degree of hypoglycemia was followed promptly by a reduction in arteriovenous difference, perhaps by virtue of some rebound mechanism set in play by the hypoglycemia.

Further indications of a role of insulin in fat formation have been obtained. Renold, Marble & Fawcett (78) have shown that injection of insulin locally into a fat depot was followed by hypertrophy of the fat body and by increased concentrations of glycogen in the adipose tissue. Similar effects were observed following systemic as well as local injections of insulin. Balmain and co-workers (79) report that insulin added *in vitro* to slices of lactating mammary gland would increase the R. Q. to values very greatly above 1.00. This occurred in presence of glucose and acetate, to a less extent with glucose alone, but not with acetate alone. It may be noted also that in the data of Villee & Hastings (51), the effect of insulin *in vitro* on the diaphragm was in every case to increase greatly the amount of labeled glucose which could not be accounted for by oxidation or by glycogen formation, so that possibly some increase in fat formation may have occurred.

Chaikoff & Forker have provided conclusive demonstration of the effect of insulin on nitrogen balance (80). In diabetic dogs on constant diet, reduction of insulin dosage was followed by loss of nitrogen, the nitrogen balance being nearly linear to the quantity of insulin given. Glucose excretion increased disproportionately. In diabetic men, in whom the intravenous catheter technique was applied, Bondy *et al.* (81) observed increased output of urea and glucose by the splanchnic area such that gluconeogenesis from

protein could account for the increase in glucose production. The administration of insulin was followed by simultaneous reduction in both urea and glucose liberation. Colenbrander (82) could not confirm earlier reports of an effect of insulin *in vitro* on urea or ammonia production by liver slices.

Levine *et al.* (83) suggest that one of the functions of insulin is to promote the removal of carbohydrate from the blood and extracellular fluid into the cells. In eviscerate nephrectomized dogs, the administration of insulin appeared to increase the volume of distribution of injected galactose (otherwise not utilized in such a preparation). The fall in blood (serum?) phosphate after insulin was suggested to follow the removal of carbohydrate, since in depancreatized dogs, phosphate was removed after fructose administration but not after glucose unless very high blood sugar levels were maintained (84).

Further observations on the "insulinase" system have been presented by Broh-Kahn, Mirsky & Simpkin. Force-feeding of large amounts of carbohydrate did not affect the inactivation of insulin by extracts made from the livers of the animals (85). The chronic injection of liver extracts into rabbits was followed by lowering of the fasting blood glucose levels and by increased sensitivity to insulin; whether this was a result of specific reduction in "insulinase" activity was not certain (86). Weisberg *et al.* (87) reported that insulin given by the splenic vein was about half as effective as when given via the femoral vein. The rate of inactivation of insulin by the liver of the dog appeared to be about .02 to .04 unit per kg. per hr.

In rats force-fed high carbohydrate diets for some time, enlargement of the islets and degranulation of the β cells but no other pathological changes were seen. A small degree of glycosuria was induced (88). Peterson (89) observed degranulation of the β cells after single large injections of glucose into rats. Recovery of the islet cells required 48 hours, and glucose tolerance curves were abnormal in the intervening time.

A diet high in cholesterol was reported by McGill & Holman (90) to induce higher blood cholesterol levels in diabetic rabbits than in normal; atheromatous lesions were much less frequent in the diabetic animals. Duff & Payne (91) observed equally high cholesterol levels in the blood of diabetic and normal rabbits fed cholesterol, but much greater increases in neutral blood fats in the diabetic animals; they suggest that this change may confer some protection against the atheromatous changes. After alloxan injections in rabbits, Swell *et al.* (92) reported only temporary increases in blood cholesterol levels, with normal values two to three weeks after treatment at a period when blood glucose values were still elevated. A persistent increase in tributyrinase content of serum was seen in alloxan diabetic rats (93).

Mechanism of insulin action.—The view that insulin may affect the oxidative release of energy from carbohydrate has received support of a more direct nature than has been available in the past. Goranson & Erulkar (94) observed that the rate of aerobic phosphorylation of creatine by heart muscle and by brain homogenates (in the presence of succinate or malate) was

slower in tissues from diabetic animals than in those from normal, and that pretreatment with insulin restored the rates to normal. Acetylation of aminobenzoate was found by Charalampous & Hegsted (95) to be significantly diminished in severely diabetic rats on high carbohydrate diets; this process could be restored to normal rates (but not increased in normal animals) immediately on the administration of intermediates of the citric acid cycle or by ATP, and over a longer period of time by treatment with insulin. On high fat diets or in fasting, acetylation rates in the diabetic rats were normal. Hastings and his co-workers have reported in a series of papers (51, 96, 97, 98) that carbon dioxide production from C^{14} -labeled pyruvate was diminished in heart and diaphragm slices from diabetic rats and also from labeled glucose in diaphragm. The addition of insulin *in vitro* increased the oxidation of pyruvate in the diaphragm of diabetic rats and of glucose in tissues from normal animals. Bartlett *et al.* (99) also noted increased oxidation of labeled glucose in presence of insulin in normal diaphragm. Cohen (288) indicated that insulin added *in vitro* increased the rate of anaerobic glycolysis. When a liver extract was incubated with yeast hexokinase in presence of α -keto-glutarate, the disappearance of inorganic phosphate was augmented by insulin in some instances (100). According to Broh-Kahn *et al.* (101), this effect could not be explained as due to inhibition of the soluble adenosinetriphosphatase of liver.

Further confirmation has appeared of earlier observations of decreased glycogen formation from glucose in the diaphragm of diabetic rats and of the effects of insulin *in vitro* on this process (51, 97). In adrenalectomized-diabetic animals, the rate of glycogen formation and of glucose uptake by diaphragm was increased over normal (51). An effect of insulin has been reported also on glycogen formation in strips of abdominal muscle (102). An interesting new procedure for the demonstration of insulin activity *in vitro* has been described by Stadie *et al.* (103, 104). When a piece of isolated diaphragm is placed in an insulin-containing medium for a brief period (10 sec. or more), then removed, rinsed well, and incubated in a glucose medium free of insulin, the usual enhancement of glycogen synthesis by the insulin is fully manifest. The authors consider that a chemical combination of insulin with the tissue must take place.

It has been widely supposed that these effects on glucose uptake result from actions of the hormones on the hexokinase reaction, the phosphorylation of glucose by ATP. However, although this reaction is essentially irreversible, its rate is not necessarily the limiting factor in the uptake of glucose by surviving "intact" tissues. In recent experiments on isolated enzyme systems, there has been no confirmation of earlier reports of effects of insulin or of cortical hormones or pituitary factors on hexokinase activity. Christensen *et al.* (105), studying the activity of hexokinase obtained from rat erythrocytes, could demonstrate no effects of insulin or cortical extracts added *in vitro*, nor could they show any difference in the rate of activity observed when the preparations were made from blood cells of diabetic or of hypophysectomized rats. An effect of added insulin on muscle hexokinase

was observed in only 1 out of 12 extracts made from the tissues of severely diabetic rats (106). With extracts made from the muscles of depancreatized cats, Stadie *et al.* (107) also observed no action of added insulin or cortical extract or of both hormones added together. These authors found that the presence of small amounts of glycogen in the muscle extracts could lead to erroneous conclusions concerning the rate of phosphorylation of glucose in such a system. This may afford a possible explanation of the inconstant apparent inhibition of hexokinase activity previously reported for extracts made from the tissues of diabetic rats. In view of these failures to affect the performance of isolated hexokinase enzyme systems, it may perhaps be suggested that the action of insulin in increasing glycogen deposition in tissue slices may be brought about by regulation of the rate of energy supply, possibly through the rate of provision of ATP required for phosphorylation.

Alloxan and other chemical diabetogenic agents.—In further investigations of the mechanism of the production of hypoglycemia after alloxan, Bailey *et al.* (108) observed no changes in the islet cells nor any diabetic responses when the alloxan was injected into rabbits during temporary occlusion of the pancreatic blood supply; but nevertheless, severe hypoglycemia was seen in several of the animals so treated. On the other hand, in rabbits previously made diabetic with alloxan, a subsequent injection of this material did not affect the blood glucose (109). Wrenshall *et al.*, reporting on extensive experiences with the effects of alloxan in dogs (110), noted hypoglycemia in about one-third of the animals which had been depancreatized immediately before experiment. In intact dogs, the degree of degranulation of the β cells after alloxan could be correlated with the apparent loss of insulin from the pancreas. No effect of alloxan on the rate of glycogenolysis was seen in isolated perfused livers of cats (109). However, Carrasco-Formiguera & Mendoza (111) reported inhibition of glyconeogenesis from lactate in the livers of rats in the hours immediately following alloxan administration and suggested that failure of glucose formation might be in part responsible for the hypoglycemic phase. Thus, an extra-pancreatic factor (possibly the result of damage to the liver) may be in part responsible for the hypoglycemic phase after alloxan, but the release of insulin from the islets seems at least equally important. Molander & Kirshbaum (112) reported the impairment of glucose tolerance but normal histological appearance of the islets following repeated injections of small amounts of alloxan in the rat.

Griffiths (113) has extended his observations on the production of diabetes by the administration of uric acid. In wild rabbits placed on diets low in sulfur-containing amino acids so that blood glutathione levels were low, large intravenous doses of uric acid (but not of xanthine nor uracil) induced histological changes in the islets, reduction of the insulin content of the pancreas, and a temporary diabetic state. Rats treated similarly showed no such changes. Collins-Williams & Bailey (114) were unsuccessful in attempts to duplicate these observations in rabbits, but as pointed out by Griffiths, the animals they used were of a very different strain (domestic) and were also probably so anemic as to withstand poorly the deficient diet. Diabetogenic

activity of large doses of dehydroascorbic and dehydroisoascorbic acids, similar to the effects of alloxan, were reported by Patterson (115) in young rats. These substances resemble alloxan in their tri-keto structure. Kadota (116), considering that agents which reacted with zinc might have actions similar to alloxan, administered a variety of such compounds to rabbits. He found that two of these, oxine (8-hydroxyquinoline) and dithizone (diphenylthiocarbazone), were potent diabetogenic substances. The usual triphasic blood sugar responses, lesions in the β cells, and permanent diabetes were observed. Potentiation of alloxan action by methylene blue administered immediately before it was reported by Lazarow & Liambeis (117).

In studies of the rabbit lens after alloxan administration, Waters (118) observed persistent reduction of the concentrations of total sulfhydryl groups in this tissue but not of free glutathione or of ascorbic acid. Presumably the protein-SH groups had been altered. No relationship of these changes to the incidence of diabetes or of cataract was noted.

Hyperglycemic factor.—Pincus (119) has summarized the evidence bearing on the hyperglycemic factor (HGF) which is extractable from pancreas and which tends to accompany insulin during its fractionation. Starting with amorphous insulin, Sutherland *et al.* (120) have prepared a concentrate of the material 10 times as active as the original; Kazal *et al.* (121) report the separation of the bulk of the HGF from insulin in one of the steps of insulin manufacture. In experiments with various insulin preparations, Weisberg *et al.* (122) reported diminution or absence of hyperglycemic activity when these substances were given to fasted rather than to fed animals. The HGF also was ineffective in the hepatectomized dog (119). In cross-circulation experiments, Foa *et al.* (123) observed a marked increase in the blood sugar levels of recipient animals when blood from the pancreaticoduodenal vein of alloxan-diabetic donor dogs was perfused into the femoral veins of normal dogs. Since the changes were larger than when blood from the mesenteric vein was perfused, and since pancreatic blood from normal dogs was hypoglycemic, the secretion of HGF by the pancreas of the diabetic animals was suggested.

THE ADRENAL CORTEX⁵

Action of adrenocorticotrophic hormone.—Work on the mechanism of stimulation of the anterior pituitary and release of ACTH has been summarized under HYPOPHYSIS. To the factors which may effect this secretion may be added a number which have recently been investigated in some detail: thyroxin (125), anoxemia (126), surgery (127), glucose administration

⁵ The papers presented at a *Conference on the Adrenal Cortex*, held by the New York Academy of Science and Academy of Medicine in March, 1948, have since been published (124). Useful discussions of material available at that time were given on the chemistry, physiology, and bioassay of adrenal hormones by Gaunt & Eversole, the Sayers, Kendall, Dorfmann, Ingle, and Greep & Dean, and on adrenal function in man and diseases of the adrenal by Woolley, Venning and Brown, Thorn *et al.*, and Kepler.

(128, 129), insulin (129), diabetic acidosis (130), estrogens (131, 132), and a number of drugs related to aspirin and to cinchoninic acid (133). In most instances, the index of adrenocortical stimulation has been depletion of adrenal ascorbic acid or in human subjects, diminution of the number of circulating eosinophils or increase in urinary corticoids. In connection with the first of these procedures, it is of interest that the adrenal ascorbic acid of chicks was not affected by ACTH or by epinephrine, although the weight of the adrenals was increased in tests prolonged over some days (134). The adrenal ascorbic acid of infant rats was responsive to ACTH (in large amount) but not to cold or to epinephrine; whether it would have been as sensitive as that of older animals to smaller doses of ACTH was not determined (135). In guinea pigs on ascorbic acid deficient diets, the adrenal ascorbic acid was very low and the adrenals somewhat enlarged. Treatment with stilbestrol brought about much greater enlargement of the adrenals and some further depletion of ascorbic acid, but the loss of ascorbic acid was related more closely to the low initial levels than to the degree of hypertrophy (132). Evidently the relationship between the function of the adrenal gland and changes in its ascorbic acid content is as yet undefined except on an empirical basis.

The relationships of cortical function to the amount of stainable lipid in the adrenal cortex has also been studied. Fortier *et al.* (136) reported that after single injections of ACTH, the lipids, cholesterol, and ascorbic acid were all diminished, but that after prolonged administration of large amounts of ACTH, the lipids returned to normal in appearance while the other indices were still much affected. After stress of various sorts, all were said to be depleted roughly in parallel. Restoration of lipid to the adrenal may occur normally during continued stimulation by ACTH but may be inhibited in some instances by the systemic effects of prolonged stress. Maintenance of the normal lipid pattern in the cortex is one of the characteristic actions of the trophic hormone [see (138, 139)].

The question of whether the glomerular zone of the adrenal cortex is under control of pituitary ACTH has received further consideration. Greep & Deane (137) report a detailed study of the regeneration of demedullated adrenals in the rat. The subcapsular cells appear to be the source of all zones of the cortex under these conditions, and complete cortical function is restored by their proliferation under the influence of the animal's own pituitary. Jones (138) and Schweizer & Long (139), working with the mouse and guinea pig respectively, noted that after hypophysectomy the glomerular zone became quite depleted of stainable lipid, although otherwise remaining normal in appearance, and that the administration of ACTH or the grafting of pituitary tissue restored the lipid to normal. Apparently the glomerular zone is not completely independent of pituitary control even though it may be capable of an autogenous existence.

The amount of ACTH secreted by the pituitary may be to some extent a function of the protein content of the diet. Handler & Bernheim (140) showed that the eosinopenic response to epinephrine was much less in ani-

mals on low protein diets than in those on complete diets, while the effects of exogenous ACTH were the same in the two series. When an extract of lyophilized anterior pituitary powder was given to rats, the degree of adrenal enlargement was greater when the animals were given 30 per cent protein than when they were fed 5 per cent protein diets; but this difference was not seen in the absence of the pituitary, nor was there any difference in the depletion of adrenal ascorbic acid in hypophysectomized rats on the two diets (141). The results in the intact animals may perhaps be interpreted as due to additional secretion of ACTH when the crude extract was given together with adequate amounts of protein.

Nature and occurrence of adrenocorticotrophic hormone.—ACTH is scarcely detectable in normal sera by current bioassay procedures (142, 143) nor is it excreted in the urine to any extent (144). Some increase in ACTH activity of the serum was seen in patients with Cushing's syndrome (143). When injected into human subjects (142) or rats (145), ACTH disappears with great speed, but little if any is excreted (142). Most criteria indicate that the administration of ACTH in quantity to men is followed by a peak of adrenal gland activity after about three hours and of adrenal hormone action after about six hours (142). Evidence of the development of antibodies and resistance to the action of ACTH after its prolonged administration to animals has been presented by Chase (146) and by Gordon (147).

When fresh anterior pituitary tissue from the rat, pig, or man was lyophilized, ground, and extracted with saline and the material so prepared assayed for ACTH activity, the indicated potency of the dry tissue was unexpectedly high, from 8 to 20 per cent of the purified standard (148). It seems possible from recent reports, however, that ACTH activity may reside in a much smaller molecule than the purified protein preparation currently considered to be the hormone. In this case, the calculated concentration of ACTH in pituitary tissue would be reduced considerably. Li *et al.* (149, 150), and Brink *et al.* (151) have found that peptic digests of purified protein ACTH, freed of recognizable protein, are at least equal to the original material in ACTH activity. The protein may be ultrafiltered under certain conditions, the preparation obtained exceeding the original in potency [Cortis-Jones *et al.* (152)]. Using ultrafiltration and chromatography, Morris & Morris (153) have recently prepared from ox pituitaries a substance, apparently a peptide, which was 10 times as active as the ACTH protein (from hog glands); Geschwind *et al.* (153a) also have obtained increased potency in material prepared as the supernatant from trichloroacetic acid precipitation of protein ACTH. The chemistry of the smaller molecule having ACTH activity is currently under active investigation in several laboratories.

The cortical hormone.—Growing evidence indicates that the adrenal hormone secreted under the influence of ACTH is a 17-hydroxycorticosterone, possibly mainly this compound itself (compound F), or a mixture of the 11-hydroxy and 11-keto (dehydro) steroids (F and E). Mason (154) has isolated 17-hydroxycorticosterone but not the dehydro compound from the urine of human subjects after the administration of ACTH or after surgery,

and in the urine of a patient with Cushing's syndrome (178). Zaffaroni *et al.* (155) have identified both compounds in normal human urine, where they were present in minute amounts, and Schneider (156) has isolated compound E from this source. In the blood coming from the adrenal vein of dogs after the administration of ACTH, Nelson, Reich & Samuels (157) found that the principal steroid was compound F, and in the effluent from the isolated perfused adrenal of the cow, Hechter (158) reported the identification of compound F as a major steroid component. Hechter *et al.* (159) also reported the isolation of corticosterone from the effluent when desoxycorticosterone was added to the perfusing medium. Conversion of desoxycorticosterone to glycogenic material, presumably by oxygenation at the 11-position, has been observed during incubation of adrenal tissue *in vitro* (160). It seems possible that the 11-desoxy compound may be an intermediate in the formation of other adrenal steroids.

The biological properties of the soluble glucoside of desoxycorticosterone were reported to be similar to those of the acetate, indicating that the lack of effectiveness of DOCA in certain respects could not be due alone to its low solubility in body fluids (161).

METABOLIC EFFECTS OF CORTICAL STEROIDS

Carbohydrate metabolism.—The glycogenic response of rats to the administration of cortical extract was found to be the same in adrenalectomized as in adrenalectomized-diabetic animals (162). The high liver glycogen values commonly seen in fasting diabetic rats (but which are abolished after subsequent adrenalectomy) would then appear not to be the result of abnormal sensitivity to cortical hormone in the insulin deficient state, but possibly to increased secretion by the adrenal cortex. In rabbits which were "sub-diabetic" after alloxan, the glucose tolerance curve was measurably elevated after treatment with cortical extract, but that of normal rabbits was unaffected (163). In severely diabetic rats force-fed constant diets, glycosuria was not increased by the repeated injection of formaldehyde, and in those animals with moderate glycosuria initially, some decrease was seen [Ingle (164)]. The author suggests that possibly the increase in adrenal hormone secreted during this stress may have gone to supply the need of the animal to combat it. Some additional measure of cortical hormone action in these circumstances would be desirable in interpreting this interesting observation, for it is not certain whether the rate of release of cortical hormone would be notably increased in animals already "stressed" to a considerable extent, or if this did occur, whether inhibition of carbohydrate utilization could be expected in the face of a continuing stress of this type.

The possible action of 11-desoxycorticosterone (DOC) on carbohydrate metabolism has received further attention. In extension of earlier work of Ingle and others, Wick *et al.* (165) were unable to demonstrate any effect of desoxycorticosterone acetate (DOCA), given over a six day period, on the glycosuria of diabetic rats either treated with insulin or not. Verzář and his colleagues have reported that although this steroid will not increase

glycogen stores when given acutely, it will do so if it is given over a sufficiently long period of time (166, 167, 168). In this work, untreated "adynamic" adrenalectomized rats were compared with those which had received DOCA over periods of days or weeks. The glycogen contents of the tissues were reported as very low in the untreated rats, whether unfasted or fasted and then fed glucose, while after the steroid treatment, the values were in the normal range. This would be expected if the DOCA treatment had allowed maintenance of the food intake (no data was supplied on this point) and general condition of the animals, since rats in adrenal insufficiency eat poorly, would probably not be able to absorb much of the hypertonic (50 per cent) glucose solution fed them in some of the experiments, and in any case, may lose tissue glycogen rapidly as they approach shock states. The authors further report that very large (narcotic) doses of DOCA inhibit glycogen formation after feeding glucose (169). No estimate was offered of the amount of glucose which could have been absorbed from the hypertonic solution under these conditions. It should be noted that the methods employed here for sampling and preparing the tissues for analysis (pithing and bleeding the animals, delay in placing the samples in alkali) were those known to lead to large losses of muscle glycogen, so that the figures given probably are valid only to an order of magnitude.

In vitro studies indicate that several steroids, including cortical hormones, DOC, androgens, and related compounds, may affect the metabolism of tissue slices.⁶ Hayano *et al.* (170) and Eisenberg *et al.* (171, 172) have found that DOC or androgens added to slices of liver, kidney, diaphragm, or brain or to brain homogenates depressed the oxygen consumption considerably. This was not due to inactivation of the cytochrome-cytochrome oxidase system (170). In rat diaphragm (98, 173) and in abdominal muscle of mice (174), DOC or cortisone⁷ inhibited the increase in glycogen formation usually seen in presence of insulin and glucose, and in the absence of glucose, increased the rate of glycogenolysis. All of these effects were obtained only with rather high concentrations of steroid, and in view of the reduction in oxygen consumption noted above, may possibly have resulted from non-specific toxicity. On the other hand, Chiu & Needham (175, 176) have reported that cortical extract, cortisone, or DOCA may inhibit glycogenolysis and enhance the new formation of total carbohydrate in liver slices. Smaller amounts of the steroids were employed than in the experiments mentioned above, and no inhibition of oxygen uptake was seen. Extension of these observations would be of much interest.

Levine, Simpkin & Cunningham (177) noted that the sensitivity to insulin of rats which had been eviscerated and adrenalectomized was of about the same order as that of control eviscerate preparations, and they conclude that most of the increased sensitivity to insulin after adrenalectomy is the result of diminution in gluconeogenesis.

⁶ See also under HYPOPHYSIS, *Experiments in vitro*, and under *Mechanism of insulin action*.

⁷ 17-hydroxy-11-dehydrocorticosterone, compound E.

The alterations in metabolism of a patient with adrenal hyperplasia associated with diabetes have been reported in detail by Sprague *et al.* (178). As judged by the blood glucose and glycosuria, the diabetes was rather mild, but was relatively resistant to insulin; the nitrogen balance was consistently negative; and alkalosis was prominent. Compound F was isolated in considerable quantities from the urine of this patient. These findings are consistent with what is known of the effects in animals of overdosage with 11-oxygenated corticosteroids. The consistent production of glycosuria in normal men given ACTH (50 mg. per day) was reported by Conn & Louis (179). In one instance in which ACTH was given in large amount to a patient suffering from acute pneumonia, glycosuria which was apparently wholly renal in origin was induced (180). Desoxycorticosterone glucuronide was also observed to diminish the tubular reabsorption of glucose in dogs and in human subjects (181). As Conn has previously indicated, it is likely that both renal and extrarenal factors are involved in the production of glycosuria after ACTH or cortical steroids. Some interesting observations have been reported by McQuarrie *et al.* on the treatment with ACTH of children with non-Addisonian hypoglycemia (182). Elevation of blood sugar and remission of symptoms occurred, but no signs of diabetes developed. The usual changes in electrolytes, eosinophils, uric acid excretion, and urinary corticosteroids were seen as in the adult treated with the hormone.

Fat metabolism.—Stoerk & Porter (183) reported that adrenalectomized rats treated with salt and in good nutritional status were able to maintain normal stores of body fats. If the animals were partially starved, however, the neutral fats of the body were depleted more rapidly than in control normal animals. Treatment with cortisone prevented this loss of fat, but DOCA did not. Earlier reports of loss of body fat after adrenalectomy, hence, were attributed to diminution of food intake in the conditions of those experiments. Similarly, in histological studies in rats and mice, Fawcett & Jones (184) observed after hypophysectomy an atrophy of the brown fat which was restored by treatment with ACTH or mitigated extensively by the feeding of adequate high-calorie diets. In rats on high fat diets, increases in the stainable neutral lipid of the brown fat after ACTH were seen in normal but not in hypophysectomized animals (185). In work to be published, Welt & Wilhelmi (186) observed a marked increase in the rate of incorporation of deuterium from the body water into the carcass and liver fats of adrenalectomized rats fed high-carbohydrate, low-fat diets. Also, diminution in the deuterium uptake was noted in normal rats given ACTH or growth hormone. In the adrenalectomized animals, the total body fat was well maintained and did not change in the course of the experiment, so that both increased formation of fat from carbohydrate and increased utilization of fat were indicated. Such a condition could provide an explanation of the increased loss of body fat on restricted diets, noted above, and it could also explain the resumption of carbohydrate utilization seen in adrenalectomized-diabetic animals; the converse situation, inhibition of fat formation from carbohydrate by excess cortical hormone, might also be

responsible for the glycosuria which occurs in treated animals force-fed high carbohydrate diets.

Reports of the effects of adrenal hormones or ACTH on the mobilization of fat to the liver are conflicting; after ACTH, the liver fat was said to be increased in rats (46), increased (187) or unchanged (48) in mice, and not affected in guinea pigs (188), while corticosteroids had but little effect in adrenalectomized mice (187). Treatment of patients with Addison's disease with 100 mg. of cortisone per day resulted in small increases in the post-absorptive blood ketone levels during the early stages of observation. Although the effect was consistent, it was so slight as to be of questionable physiological significance (189).

A considerable decrease in plasma cholesterol particularly of the esterified fractions was observed in human subjects after several days of treatment with ACTH. Since a similar effect has not been noted after the administration of cortical hormone, the authors suggest that it may perhaps have been the result of withdrawal of cholesterol by the adrenal gland for the formation of corticosteroids (190).

Nitrogen metabolism.—Continuing earlier studies on the rate of urea formation in the nephrectomized rat, Engel (191) has found that insulin in moderately large dosage leads to a delayed increase in the rate of nitrogen catabolism. When adrenal extract was given before or with the insulin, the increase then became immediate. Glucose administration prevented the increase in either case. These data were interpreted reasonably to mean that insulin hypoglycemia calls forth a catabolic response for which increased adrenal activity is permissive but for which the adrenal hormone is not itself the responsible agent. In adrenalectomized eviscerated rats, Bondy (192) observed a considerable diminution in the rate of release of amino acids to the plasma. A small amount of cortical extract sufficed to restore the rate to normal, while a larger quantity increased the rate of protein breakdown in normal eviscerate rats. The latter action was abolished by the administration of glucose in quantity. Similarly, Kline (193) observed a diminution in the rate of release of nitrogen from diaphragm of adrenalectomized rats when this tissue was incubated *in vitro* and restoration to normal rates on pretreatment of the animals with cortical extract. On the other hand, Ingle *et al.* (194) found it difficult to demonstrate any marked increase in nitrogen loss when cortical extract was given to adrenalectomized rats fed an adequate balanced diet. It would appear that the cortical hormone may affect the net loss of protein from the tissues when the rate of this process would be high, but that when the nitrogen metabolism of the animal is properly supported by adequate metabolism of carbohydrate or perhaps by replacement of nitrogen, the cortical hormone has no obligatory catabolic action.

The effects mentioned above could have resulted from action of the cortical hormone either on the anabolism or on the catabolism of the tissue protein. In an attempt to separate these two phases of nitrogen metabolism, Hoberman (195) has made an extensive study in rats of the effects of several

hormones on the rate of excretion and, by inference, of the rate of incorporation into protein, of isotopic nitrogen from administered N^{15} -glycine. Sprinson & Rittenberg (196) showed in man that the excretion of isotopic nitrogen from glycine followed a time curve which could be explained if the administered nitrogen mixed immediately with a homogeneous pool (presumably mainly of amino nitrogen) from which catabolism and excretion of nitrogen as well as synthesis of protein took place continuously and into which also unlabelled nitrogen from the body protein entered. On the assumption that the labeled nitrogen which was not excreted within several days (when the maximum of the curve of excretion was reached) had been incorporated into tissue protein, figures for the rate of synthesis of protein and also of the pool size could be derived. In the fed animal in a steady state, the rate of synthesis would be equal to the rate of protein breakdown. In the present experiments, Hoberman utilized a similar procedure but applied it to fasting rats rather than to fed animals. Since in the absence of nitrogen in the diet, the excretion of nitrogen must equal the breakdown of body protein less the amount of nitrogen resynthesized, it was possible under these circumstances to obtain values for the rates both of anabolism and of catabolism of body protein.

The further assumption was made by Hoberman that both synthesis of protein and catabolism of amino acids (not of body protein) are first order reactions with respect to the pool size and that the first order constants seen in various endocrine states are representative of the rates of these processes. The basis for this assumption is hard to find, and indeed, data of Sprinson & Rittenberg obtained on normal rats fed various amounts of protein in the diet show clearly that neither process can be related to the pool size in this way. Among the 14 experimental groups reported by Hoberman, it may be shown by calculation from the data presented that the apparent mean pool size varied widely, from 21 mg. per 100 gm. body weight in thyroidectomized-adrenalectomized rats through 65 mg. for normal to 90 mg. for diabetic rats. In view of these differences and in the absence of evidence that rates of removal of amino acid from the pool are proportional to the pool size in any given set of circumstances, it may be misleading to compare the rates of excretion and of anabolism of nitrogen only on the basis of the fractions of the pool so metabolized, as the author has done. To facilitate study of this data, the present writer has prepared a summary table containing calculations of rate of synthesis and of pool size in addition to the other figures (Table I). The experiments reported by Hoberman may be further criticized for their dependence only on the metabolism of a single possibly unrepresentative amino acid and for the fact that the fitness of the equations used rests only on the curve of nitrogen excretion without verification from analytical data obtained in the animal body. Nevertheless, the method offers a new approach to the solution of an important set of problems, and the data suggest provisionally a number of interesting conclusions.

According to the analysis used by Hoberman, in the fasting adrenalect-

tomized rats, there was no change in the fraction of the pool which was catabolized to urea but an increase in that synthesized to protein. The calculated pool size was smaller than in the normal rats, however, so that the rate of catabolism of amino acids (which is represented by nitrogen excretion) was diminished, and no change or a slight decrease in actual rate of

TABLE I
ENDOCRINE EFFECTS ON PROTEIN METABOLISM IN FASTING RATS, FROM THE
EXCRETION OF ISOTOPIC N [AFTER HOBEBMAN (195)]

Group (Av. of 6 obs. except as noted)	Urinary Nitrogen	Synthe- sis of Protein	Protein Break- down E+S (=k ₁ P)	Amino N Pool	Catab- olism of Amino Acids k ₁	Anabo- lism of N k ₂
	E	S*		A*		
	mg. N per 100 gm.		per hr.	mg. per 100 gm.	per cent A per hr.	per cent A per hr.
Normal	2.11	4.14	6.25	65.6	3.25	6.31
Adrenalectomized	1.80a	3.77a	5.56a	52.3a	3.48	7.24a
Adrenalectomized + Growth Hormone [5]	1.52b	4.08	5.59	59.1	2.51b	6.79b?
Adrenalectomized + Compd. E	3.34b	3.53	6.87b	66.6b	5.05b	5.38b
Thyroidectomized	2.40a	2.43a	4.83a	42.0a	5.79a	5.82
Thyroidectomized + Growth Hormone	1.64b	3.45b	5.10	47.3	3.67b	7.36b
Hypophysectomized	2.04	2.53a	4.57a	36.9a	5.63a	6.93a?
Hypophysectomized + Growth Hormone	1.36b	3.03b?	4.40	40.9	3.67b	7.51b
Hypophysectomized + ACTH	3.12b	2.58	5.70b	52.6b	6.00	4.85b
Thyroidect.-Adrenalect.	1.42a	1.48a	2.90a	21.1a	6.63a	7.13a
Thyroidect.-Adrenalect. + Compd. E	3.97b	1.67	5.64b	46.8b	8.50b	3.72b
Diabetic [4]	5.80a	2.75a	8.85a	89.7a	6.47a	3.10a
Adrenalect.-Diabetic [4]	2.47b	3.20	5.67b	81.4	3.11b	3.75
Av. stand. dev. within groups*	.33	.44	.53	10.3	.77	.73

a—significantly different from normal ($p < .05$); b—significantly different from respective control group; ?—approaching significance.

* Calculated from the data of Hoberman (195).

synthesis was indicated. The rate of breakdown of body protein was diminished somewhat. Conversely, in the series in which ACTH or cortisone was given (to adrenalectomized, hypophysectomized, or thyroidectomized-adrenalectomized rats), the nitrogen excretion was always much enhanced, the pool size was enlarged, and hence the fractional rate of catabolism of pool nitrogen only increased moderately in two of the three instances. The fraction of the pool undergoing synthesis was diminished but the amount of synthesis was unchanged. The source of the increased nitrogen loss was apparent in every series in a considerable increase in the calculated rate of protein breakdown. A further indication of the role of the adrenal hormone

in protein catabolism was seen in the diabetic rat; here the rate of protein breakdown was much increased and that of synthesis diminished, while after adrenalectomy of the same animals, protein catabolism was slowed to normal but no change was seen in the rate of synthesis. A similar conclusion as to the role of adrenal hormone was drawn by Margen *et al.* (197), who found in a patient with Cushing's syndrome that the excretion of labeled sulfur from S³⁵-methionine was normal and the uptake of sulfur into the plasma proteins somewhat increased. In the absence of obvious defect in protein synthesis, the persistent negative nitrogen balance characteristic of this disease was then attributed to increased catabolism of the tissue proteins.

Cagan *et al.* (27) reported some increase in the amino acid oxidase activity of liver homogenates after either *in vivo* or *in vitro* addition of cortical extract. The removal of administered amino acids from the blood was found diminished in adrenalectomized rats, but this might have been a result of circulatory difficulties since a large amount of hypertonic solution was given intraperitoneally in this case. Two earlier observations of effects of cortical hormones on the plasma proteins could not be confirmed: Milne & White (198) could demonstrate no action of cortical extract or of x-radiation on the electrophoretic pattern of mouse plasma, although the total protein concentration was increased, and Schwartz & Engel (199) could find no relationship of the serum content of amino-peptidase (for leucyl-glycylglycine) to excess or deficiency of adrenal hormone in human subjects.

Salt and water metabolism.—Detailed studies of the electrolyte concentrations in the tissues (liver, muscle, and testis) of adrenalectomized rats and of the effects of treatment with desoxycorticosterone have been reported by Cole (200, 201). The effects of DOC in reversing some of the changes seen were considered secondary to changes in plasma sodium and in concentrations of nondiffusible molecules within the cells. In the dog, Gaudino & Levitt (202) found the most marked changes in adrenal insufficiency to be diminution in the extracellular water volume and increase in the intracellular fluid, with relatively small changes in the plasma volume or in the total water of the body. Flanagan *et al.* (203) noted the loss of extracellular sodium in adrenal insufficiency to be greater than could be accounted for by excretion of sodium, and the increase of salt in body fluids on recovery, greater than the positive balance from the salt fed. The tissues underwent comparatively small changes in electrolyte composition, so that the authors suggested the existence of some labile store of sodium and chloride in the body, possibly in bone.

Following earlier demonstrations of the effects of DOC on the excretion of salt in the sweat [confirmed recently by Robinson *et al.* (204)], Conn & Louis (179) have now found that ACTH given to normal men also reduces markedly the amounts of sodium and chloride lost in the sweat. Since, during the initial phases of exposure to heat, changes in nitrogen and uric acid excretion and in salt in the sweat parallel those seen after the administration of ACTH, Conn & Louis suggest that increased secretion of adrenal

hormones may play an important part in acclimatization to heat. The use of estimations of the concentrations of salt in the sweat was also suggested as a clinical test for adrenal function. No evidence that increased adrenal activity resulted from salt deprivation alone (without heat) could be found by Daughaday & MacBryde (205).

In acute tests in adrenalectomized rats given small amounts of radio-active sodium salts, Dorfman (206) found that following as little as 1 μ g. of DOC, excretion of sodium was diminished; a closely related steroid, pregnenole trione, was slightly active, while 17-hydroxycorticosterone increased sodium excretion at intermediate dosages. Further observations indicating some degree of opposition between DOC and oxygenated steroids on sodium metabolism were reported by Woodbury *et al.* (207). The serum sodium and also the threshold for electroshock seizures were increased in rats by treatment with DOCA, increased slightly by ACTH, and unaffected by cortical extract; but when ACTH or the extract were given with the DOCA, the sodium level and thresholds were restored to normal. Diminution of serum potassium levels after DOCA were unaffected by simultaneous treatment with the adrenal hormones. An observation which may be interpreted similarly was made in human subjects by Soffer *et al.* (208). When DOCA was given to normal subjects, the usual retention of salt was seen, but in patients with Cushing's syndrome, the steroid either was without effect or increased the excretion of salt. The explanation of the paradoxical relationship is not yet at hand. Sprague *et al.* (253) observed in man that chronic treatment with ACTH or cortisone induced sodium retention in the early stages and some loss later.

The relation of the adrenal cortical hormone to water balance has been discussed in an excellent review by Gaunt *et al.* (209). The authors point out that adrenocortical hormones are necessary for rapid excretion of water and that adrenal extracts are active diuretic agents, particularly in states of overhydration. In the absence of the adrenal, extrarenal factors also may affect excretion of water. Evidence for effects of adrenal hormones on tubular reabsorption of both water and sodium and chloride ions have been brought forward. In adrenalectomized rats (210, 211) and dogs (212) which are well hydrated and in good condition, the glomerular filtration rate may be normal.⁸ Roemmelt *et al.* (212) observed further in the adrenalectomized dog that tubular reabsorption of salt was diminished at low or intermediate salt loads, but as in the case of water, the capacity to excrete maximal loads was diminished. This was interpreted to be in accord with the view that the adrenalectomized animal suffers from the unopposed action of pituitary antidiuretic hormone, since ADH increases sodium and

⁸ The glomerular filtration rate is, of course, diminished in conditions of acute adrenal insufficiency. Lockett (213) has found that changes in filtration rate begin at a time when the blood nonprotein nitrogen is still normal, but when the blood pressure is beginning to fall and hemoconcentration and increased circulation time have become evident.

chloride excretion when urinary concentrations of salt are initially not exaggerated, but decreases the excretion when the concentrations are at their maximum, in proportion to the reduction in urine volume. In adrenalectomized rats, increased concentrations of an antidiuretic hormone-like agent in the blood and also an increased sensitivity to administered ADH, have been demonstrated by Birnie *et al.* (214). It is possible not only that the physiological action of ADH is enhanced in adrenal deficiency but also that there may be in this condition either increased secretion or diminished destruction of the pituitary factor. Alterations in the excretion of potassium after adrenalectomy or adrenal hormone were believed not to be related to pituitary function but to be the result of a specific alteration in the tubular reabsorption of this ion (212, 215). Changes in the blood electrolytes commonly seen in other animals after adrenalectomy have been reported also in the goat (216). The animals died usually within a week, without evidence of hemoconcentration or unusual hypoglycemia.

Muscle.—Voegtli (217) has reported that the isolated diaphragm from rats in adrenal insufficiency has a normal work capacity, but that changing the ionic environment to one lower in sodium and higher in potassium than normal would reduce greatly the work capacity of normal tissue; he suggests, therefore, that the adynamia characteristic of untreated adrenal deficiency is the result of altered salt concentrations in the tissues. This conclusion is not in accord with the well known inability of salt therapy or DOC treatment to restore work performance. In adrenalectomized rats infused intravenously with adrenal extracts during repeated stimulation of the muscles of the hind limbs, the amount of hormone required for normal responses was very high, about 20 ml. per 24 hr., or an amount representative of 800 gm. of beef gland per rat per day (218). In healthy adrenalectomized dogs maintained on small amounts of adrenal extract, the pressor response to epinephrine and to other drugs was decreased, apparently due to diminished responses of the heart or of the vascular smooth muscle (219). The vasomotor response to central sciatic stimulation was also reduced after acute adrenalectomy and restored by adrenal extract (220). The diminished neuromuscular responses of adrenalectomized rats could not be explained by changes in cholinesterase concentrations in tissues or serum (221).

Reactions of mesenchymal tissues.—Effects of adrenal hormones on a variety of tissues of mesenchymal origin have now been noted, but they are as yet ill understood. Since these reactions must underlie many of the phenomena of resistance to stress and altered reaction to disease which are conferred by adrenal hormones, their eventual explanation is of the greatest importance.

The best known of these actions is the eosinopenic and lymphopenic response to adrenocortical hormones. Detailed accounts of the effect on circulating eosinophils in the rat, dog, and man (222) and mouse (223) have now been published. Changes in the eosinophil count are probably the most sensitive indicator available of adrenocortical activation; in some

animals mild stimulation, such as by ordinary handling, suffices to produce a full response. The eosinophilia characteristic of infection with *Trichina spiralis* also may be abolished by treatment with cortical extract or epinephrine (224). Lymphopenia and atrophy of the lymphoid tissue in animals given an excess of cortical hormone have been confirmed (225). Herlant (226) reports, as have others, that adrenalectomy prevents the severe caryoclasia of lymphoid tissue usual after stress (cold, forced work, formaldehyde injections). In this case, the administration of cortical extract alone was found to have little effect on the lymphoid tissue of adrenalectomized rats, but when the hormone was given to stressed adrenalectomized animals, extreme caryoclasia was seen. This interesting observation suggests a permissive rather than an active role of the adrenal hormone in the dissolution of lymphoid tissue, a situation resembling that seen with respect to the action of cortical hormone on the catabolism of protein in other tissues. Some acceleration of lymphocytolysis by cortical extract *in vitro* was reported by Hechter & Johnson (227). Gordon & Katsh present evidence that adrenal hormones may affect the structure and phagocytic activity of the macrophage system (228).

Inhibition of hyaluronidase by adrenal hormones has been established by several investigators (229 to 236). Following earlier reports of the action of cortical extract on the spreading of india ink given with the enzyme to mice, Opsahl (229 to 232) has shown that the extract was effective also in rabbits and that cortisone and 11-dehydrocorticosterone were active, but testosterone, progesterone, and estradiol benzoate were not. The inhibition of hyaluronidase activity could be seen when the hormone was given systemically or locally, the latter procedure being the more effective. Seifter *et al.* (233, 234) demonstrated that ACTH or cortisone would diminish the action of hyaluronidase on the permeability of the urinary bladder, lens capsule, or synovial membrane of the rabbit. No such effect was seen with DOCA. In human subjects, the cutaneous spread of fluorescein given with hyaluronidase was inhibited by prior administration of adrenal steroids or epinephrine, or by surgical trauma (235). The area of spreading of india ink with hyaluronidase in the skin was noted also to be diminished in untreated diabetic dogs (237).

Anaphylactoid and other types of hypersensitivity reactions can be inhibited by adrenal hormones. In rats, which undergo a response to intraperitoneal injection of egg white that is similar in appearance to an allergic reaction, both ACTH and cortisone but not DOC suppressed the reaction completely (238). The administration of ACTH before the second injection of a bacterial filtrate nearly completely prevented skin reaction characteristic of the Schwartzman phenomenon (239). Dermal or systemic reactions to antigens in other animal experiments were in some instances inhibited by cortisone, in others not (240, 241, 242). In human subjects, a variety of severe hypersensitivity reactions may be suppressed by the administration of ACTH or cortisone (243). The view that cortical hormone increases the

titer of antibodies in the blood by release of these substances from the lymphocytes has been challenged (244, 245, 246), although the anamnestic response to cortical extract in rabbits immunized to sheep cells was confirmed (246). From the data so far available, it would appear probable that the adrenal hormone does not intervene actively in the development of antibodies, but that it affects the inflammatory response of the tissues to the immune reaction.

Ragan and co-workers have studied the effects of cortical hormones on wound healing (247, 248, 249). In human subjects and in rabbits given cortisone or ACTH, there is notable inhibition of the development of granulation tissue, delay in healing, and delay also in the repair of bone fractures. Normal granulation and collagen development after turpentine injections were reported in adrenalectomized-castrate rats (250). Whether the action of the adrenal steroids on wound healing is related to inhibition of hyaluronidase is not yet known.

Clinical Studies.—Following the announcement in April, 1949, of the remission of symptoms of arthritis on treatment with ACTH or cortisone, an extensive literature has accumulated on the clinical effects of adrenal hormones and related steroids in a variety of diseases. For citations to this work, the reader is referred to the useful summary prepared by Thorn *et al.* (251), and to the preliminary reports of clinical trials with ACTH, edited by Mote (252). The most detailed accounts available of the actions of cortisone and ACTH in man are those of Hench, Sprague, and co-workers (253, 254), McEwen *et al.* (255) and Thorn *et al.* (256). From the present evidence, it appears that the diseased states in which adrenal hormones may be the most useful include acute rheumatic fever, arthritis, status asthmaticus, serum sickness, exfoliative dermatitis, and related states of hypersensitivity. According to Thorn *et al.* (251), the adrenal hormones may "intervene in the manifestations of hypersensitivity of the body [to] inhibit the altered reactions of cells [that] so often prove more harmful than the direct toxic effects of the sensitizing agents themselves." Whether this intervention is physiological or pharmacological in nature is not yet known. It is perhaps too soon for contraindications to the use of these powerful agents to have become definite.

ADRENAL MEDULLA

Norepinephrine.—Convincing evidence has been presented for the occurrence of norepinephrine (noradrenaline, arterenol) in the adrenal medulla and the secretion of this substance in response to splanchnic stimulation. In extracts of medullary tissue of a number of species, as well as in supposedly pure epinephrine prepared from natural sources, the ratio of epinephrine to norepinephrine has been estimated by chemical isolation and by bioassay to be on the order of two or three to one (257 to 263). In adrenomedullary tumors, norepinephrine was present in excess (264). By matching the effects of splanchnic stimulation and of mixtures of norepinephrine and

epinephrine on the nictitating membrane, Bulbring & Burn have estimated norepinephrine to constitute 20 to 80 per cent of the secreted hormone (265). The proportion of norepinephrine appeared to increase on repeated stimulation. Formation of epinephrine from norepinephrine (by methylation of the amino group) was demonstrated in perfused isolated adrenal glands and in minced adrenal tissue *in vitro* (266, 267). Sympathin released on stimulation of splenic or hepatic nerves appeared to consist mainly or entirely of norepinephrine, as judged by its biological effects (268, 268a, 268b); extracts of cattle heart also yielded mainly norepinephrine (269).

The physiological and pharmacological actions of norepinephrine as compared to epinephrine and to other sympathicomimetic substances have recently been studied extensively by several workers (270 to 273) and reviewed by Lands (274) and by Burn (275). Differential bioassay procedures have been proposed by Gaddum *et al.* (270, 276) and by Burn *et al.* (277). Although norepinephrine appears to be mainly an excitator, with less inhibitory action than epinephrine in several tests, it is not entirely lacking in inhibitory effects. Norepinephrine was reported to have about 1/100 the activity of epinephrine in inhibiting contractions in the isolated rat uterus, to have approximately the same degree of activity in inhibiting motility of the rabbit colon, in increasing vasoconstriction in the rabbit ear, and in augmenting contractions of cat spleen (270) and to be several times as active as epinephrine in affecting the denervated nictitating membrane of the cat (265).

Few studies of the metabolic actions of norepinephrine have appeared. The hyperglycemic activity has been reported to be 5 to 10 per cent of that of epinephrine (271, 278), its action in raising the oxygen consumption about one-fifth that of epinephrine in guinea pigs (279) and significantly less than that of epinephrine in man (280). If the glycogenolytic power toward muscle should also prove to be much less than that of epinephrine, the effect of adrenomedullation in preventing glycogenolysis after general sympathetic stimulation would be explicable.

Metabolic effects of epinephrine.—Lundholm has presented extensive studies of the action of epinephrine on the oxygen consumption of resting animals (281). The increase in oxygen utilization was correlated closely with the increase in blood lactic acid. Since infusion of lactate to the same blood lactate levels also increased the oxygen consumption, Lundholm suggested that the increase in metabolic rate may be secondary to release and utilization of lactate.

The intra-arterial infusion of epinephrine in man had very little effect except to produce some vasoconstriction of the skin of the perfused limb (282). In rats, infusion into the carotid artery also was ineffective, as judged by changes in the glucose, lactate, and glycogen of the blood and tissues (283). Presumably, the epinephrine must have been destroyed by the tissue to which it was delivered. Surprisingly, direct delivery of epinephrine to the liver through either the portal vein or the aortic arch also did not affect the liver glycogen and had but slight action on the blood glucose. From

this data, it would appear that epinephrine in moderate dosage had little or no direct action on liver metabolism (283).

Ingle (284) found that epinephrine noticeably decreased the tolerance for glucose in eviscerated rats, whether the adrenal glands were present or not, and also that work performance in normal eviscerate animals was diminished by the hormone. In adrenalectomized noneviscerate animals, with or without cortical extract, epinephrine had no effect on work performance (285). Griffith *et al.* (286), comparing the effects of intravenous epinephrine and glucose on the arteriovenous differences in glucose and oxygen, found no evidence for diminished utilization of glucose during short periods of infusion. However, the blood glucose fell more rapidly after glucose than after epinephrine. Inhibition of anaerobic glycolysis in the isolated diaphragm was reported after the administration of epinephrine to rats prior to experiment, but no direct action of the hormone *in vitro* was seen (287, 288).

A fall in serum potassium concentration after the intravenous infusion of physiological amounts of epinephrine was noted by Rogoff *et al.* (289). The authors suggest that the elevation in serum potassium seen after adrenalectomy may be in part related to the absence of the adrenal medulla.

THYROID GLAND

Thyroid function.—Perlmutter & Riggs (290) have estimated the uptake of radioactive iodine (I^*) by the thyroid gland in man. Appreciable differences in the gradient of iodine concentration were seen with differences in age and sex, and within any group of normal subjects, a rather wide range of variation was noted without apparent correlation with the level of serum precipitable iodine. Evidently the serum precipitable iodine constitutes only a partial reflection of the degree of thyroid activity. As expected, the uptake of iodine was low in hypothyroidism and high in hyperthyroidism (290, 306).

Meites *et al.* found no evidence for diminished thyroid function in underfed rats except in proportion to body size, nor was the secretion of thyrotrophic hormone under the influence of thiouracil affected by underfeeding (291, 292). During stress, thyroid function did not appear to be diminished (293, 294). Using changes in the thyroid gland and in rate of metamorphosis in the starved tadpole, D'Angelo & Gordon (295) demonstrated a method for detecting thyrotrophic hormone (TTH) and thyroxin simultaneously. In the rat, the serum contained large amounts of TTH but little thyroxin, while in the sera of other species, including man, the proportions were reversed. The uptake of isotopic phosphorus into the thyroid of guinea pigs was increased up to fourfold by prior treatment of the animals with small amounts of TTH, and this effect was offered as a basis of bioassay of the hormone (296). Goldberg, Chaikoff *et al.* have reported extensively on the effects of irradiation through administered I^* on the structure and function of the thyroid (297 to 300). Depending on the amount

of radiation, from little damage to complete destruction of the thyroid was seen, with but minimal effects on adjacent structures even at high dosages. Some excellent summaries have appeared on the action of TTH (301), the metabolism of iodine in man (302), and the clinical use of I* (303, 304).

Inhibition of the thyroid.—Raben (305) & Stanley (306) have found that hyperplastic thyroids are more sensitive to the inhibitory action of iodide than normal glands. Also, thiocyanate given with iodide reduced the amount of iodide present in the thyroid and allowed an increase in organic iodine. Hence, inhibition of thyroxin formation by iodide would appear to be a function of the amount of iodide in the gland rather than of the serum iodide. Wolff & Chaikoff (307) reported that inhibition of thyroid activity by excess iodide was temporary, its maximum duration in the rat being about 50 hr. As was to be expected, therefore, continued administration of iodide did not lead to increased secretion of TTH or to formation of goiters.

Isolation and identification of a naturally occurring goitrogen, 1-5-vinyl-2-thio-oxazolidone, from turnip and from brassica seeds has been reported (308, 309). The activity of this compound equalled that of thiouracil in acute tests in men and was about one-fifth that of thiouracil in 10 day tests in rats. Astwood (310) has reviewed the subject of naturally occurring goitrogens and has suggested that goiter in man may sometimes be due to the action of such goitrogens from the food. In chicks from hens fed thiouracil, enlargement of the thyroid was noted (311); similar effects of fed thyroprotein could be explained by the high iodine content of the diet (312). Failure of goitrogenic doses of thiouracil to affect the metabolic rate (313) or uptake of deuterium into tissue constituents (314) has been reported. The possible mechanism of action of thyroid inhibitors has been discussed by Pitt-Rivers (315).

Thyroid hormone.—Further observations indicating that the circulating thyroid hormone is principally thyroxin have been presented by Laidlaw (316) and by Taurog *et al.* (317). Basil *et al.* (318), using the mouse anoxia method, have measured the activity of several forms of thyroxin. The degree of activity appeared to be roughly parallel to the solubility of the substances, the sodium salt of L-thyroxin being about five times as active as free thyroxin. The L forms of the salt (318) or of the amino acid (319) were two to three times as active as the D forms. Basil *et al.* (318) concluded that all of the activity of dried thyroid powder could be accounted for by its content of natural thyroxin. Monoiodothyroxin has been identified in the thyroid gland of the rat, chicken, and sheep, where it contributed about 10 to 20 per cent of the organic iodine (320).

The metabolism of I*-labeled thyroxin or thyroglobulin has been studied by several groups of workers (321 to 324). The labeled material was found in all organs without special concentration in any tissue. The iodine was excreted largely as inorganic iodide, in part through the bile, some in the stomach, and in part in the urine. In general, the economy of the body for administered thyroid hormone was rather poor, much of the substance being destroyed within the first day or two.

The apparent formation of thyroxin after the administration of elemental iodine to thyroidectomized or thiouracil treated rats was again indicated (325, 326). Barker & Lipner (326) estimated from the effects on metabolic rate that about 1 μ g. of thyroxin was formed per milligram of iodine given. Very large amounts of nonthyroxin, protein-bound iodine were found in the plasma of the injected animals.

Metabolic actions of thyroid hormone.—The administration of thyroxin or thyroid substance to rats was followed by an increase in the hexokinase activity of leg muscle (327) and of succinoxidase in the liver (327, 328). Choline oxidase (327), xanthine oxidase (329), or cytochrome oxidase (328) were not increased, while liver lactic dehydrogenase was diminished (330). In the instances examined, *in vitro* addition of thyroxin or thyroglobulin did not affect enzyme activity (327). Hyperthyroidism led to increased concentrations of cytochrome-*c* and of pentose-nucleic acids (PNA) in the tissues, but impaired regeneration of liver tissues and enzymes, while hypothyroidism was accompanied by loss of cytochrome-*c* in several tissues, but did not affect the ability of the liver to regenerate (331). Although such data as are available do not prove the point, they do suggest that the thyroid hormone may affect metabolic rates at least in part by altering the concentrations (synthesis?) of some critical enzyme systems in the tissues.

Diminution of the rate of release of nitrogen from the tissues of thyroidectomized rats was observed in eviscerated animals (192) and in *in vitro* preparations of liver slices and diaphragm (193). In both instances, prior treatment of the animals with thyroxin restored the rates to normal. Evidently the loss of nitrogen from the tissues is not a function of temperature of the body alone but is also related to the enzyme content or to the metabolic rate of the tissues. From the data of Hoberman [Table I (195)], it appeared that both synthesis and catabolism of protein were slowed in fasting, thyroidectomized rats.

Scow, Simpson *et al.* have reported on the effects in the rat of thyroparathyroidectomy at birth and of treatment with growth and thyroid hormones (332, 333). Growth was very slow in untreated animals, was accelerated somewhat by growth hormone and markedly by thyroxin, and was nearly normal when both hormones were given. Treatment with thyroxin alone led to development of an adult hair coat, to skeletal maturation, and to some growth of the gonads. Histological changes in the pituitary were marked in untreated animals, prevented by thyroxin, and exaggerated by growth hormone. After hypophysectomy in very young rats (334, 335), the degree of growth and differentiation resembled that seen after thyroidectomy, and in the absence of the pituitary the time of closure of the epiphyses (metacarpal) was returned to normal by treatment with thyroxin (336). Weiss & Noback (337) also reported that the time of appearance of ossification centers in the rat fetus was delayed by treatment of the mothers with thiouracil, while thyroxin led to no further acceleration. From these and other observations, it seems likely that the thyroid hormone influences growth and development in part directly, particularly with respect to the

degree of differentiation of bone, and probably in part also by maintenance of normal pituitary function.

Extreme sensitivity of the metabolic rate to thyroxin was seen in thyroidectomized rats but not in animals given thiouracil; in the former, 6 $\mu\text{g. per kg. per day}$ sufficed to produced a detectable effect, while 20 $\mu\text{g. per kg. per day}$ returned the metabolic rate to normal (338). Additional data have appeared on the relationship of thyroid function to cholesterol metabolism (339, 340), to food consumption and growth (341), and to lymphoid tissue (342).

METABOLIC EFFECTS OF SEX HORMONES

The anabolic action of androgens has been further demonstrated in the rat (343 to 346), man (347), and monkey (348). From the observations of Kochakian in the rat, the male is more responsive to androgen than the female, whether the animal is gonadectomized or not (344). On chronic treatment with androgen, the increase in body weight and nitrogen retention were temporary, subsiding after 10 to 14 days (343). Growth hormone given in similar circumstances continued to act for long periods, particularly in the hypophysectomized animal. In the absence of the pituitary, testosterone was much less effective than in castrate animals, although some retention of nitrogen and increase in body weight were observed (345). It is not apparent whether the anabolic action of androgen is in part dependent on the presence of pituitary growth hormone, or if it may be independent of the latter hormone, but require the presence of adrenal or thyroid factors.

Depression of growth in rats given estrogens was reported to be largely but perhaps not entirely the result of diminution in food intake (350). Gyorgy *et al.* (351, 352, 353), have observed in rats on low-protein, high-fat diets that estrogens may exhibit lipotropic activity, particularly if some methionine is also administered. In chicks, Stamler *et al.* (354) report that prolonged administration of diethyl stilbestrol, besides increasing the plasma lipids, also increased the deposition of lipid in liver and carcass. The incidence of diabetes in partially depancreatized rats was reported to be diminished by estrogens and increased by androgens (355). The possible role of altered food intake in these conditions was not evaluated. In force-fed, depancreatized rats, stilbestrol at first increased the incidence of glycosuria; then, after some months, the blood sugar levels were lower in the treated group and the pancreatic islets were said to be hyperplastic (356). The mechanism of the metabolic actions of the estrogens is obscure. It is possibly concerned with the level of activity of the pituitary or adrenal glands and should be investigated in this respect.

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PHYSIOLOGY OF REPRODUCTION¹

By J. E. MARKEE

*Department of Anatomy, Duke University School of Medicine,
Durham, North Carolina*

Two topics in this review, histochemistry and neurohumoral relations in reproduction, have been emphasized. The other phases of the physiology of reproduction have been treated very briefly only because about 500 references must be mentioned in such a restricted space.

HISTOCHEMISTRY OF THE REPRODUCTIVE ORGANS

Hypophysis.—A study by electron microscopy of cytoplasmic granules in the anterior lobe cells of the rat hypophysis reveals no fundamental differences in the submicroscopic structure of the three basic cell types [Fernández-Morán & Luft (1)]. Normal development and cellular differentiation in the pituitary of the golden hamster conform to that in other mammals [Krol (2)]. Through the first 19 years of life, changes in the proportion of cell types in the human hypophysis do not indicate distinct histological cycles [Rasmussen (3)] that can be correlated with physiological ones.

The McManus-Hotchkiss periodic acid-leucofuchsin method of staining for polysaccharides or glycoproteins has stimulated considerable cytochemical work on the adenohypophysis (4 to 7). The basophil cells of the rat pituitary contain a glycoprotein constituent which increases greatly after castration and which fluctuates with the estrous cycle; a part of this material may be follicle stimulating hormone (FSH) [Catchpole (4)]. Other techniques [Wolfe (8)] supply cytochemical evidence of secretion of luteinizing hormone (LH) by acidophils and chromophobes in response to estrogen. Estrogen inhibits the hypophysis and induces a decrease in the relative numbers of both basophils and acidophils [Finerty & Meyer (9)]; this decrease occurs also during adolescence in the dog [Francis & Mulligan (10)]. The ascorbic acid level in the rat hypophysis increases with age (11) and adrenalectomy (12); pituitary stimulation of gonadotrophin-release in neither the rat nor the rabbit affected the normal level (11) as had been previously reported.

Changes in the human hypophysis during pregnancy include characteristic pregnancy cells, which are larger, but which apparently arise from chromophobe cells, and hypertrophied cell cords [Floderus (13)]. In the rat, mitotic activity in the hypophysis during the first three days of pregnancy and after parturition is related to the level of secretion produced by the pituitary or by the placenta [Hunt (14)].

The ovary.—The primary interstitial tissue of the ovary of the infantile

¹ This review covers the period from June, 1949 to June, 1950.

rat appears to arise as cords from closely related groups of follicles [Dawson (15)], and luteal function in the immature rat has been studied by King *et al.* (16). Cholesterol is the precursor of the steroid hormones of the interstitial cells of rabbit ovaries [Claesson *et al.* (17)]; and in the ovarian interstitium of the rat, cholesterol esters appear at about the 10th or 12th day of life [Rennels (18)]. The Swedish school (19) has continued its study of cholesterol esters in the ovarian interstitium; in adult female hypophysectomized rats, storage of "estrogen precursor" requires a combination of pregnant mare serum (PMS) and pregnancy urine (PU). Further advances in this work await the utilization of purified pituitary gonadotropins. The interstitial cells in the medullary portion of the ovary [Taber (20)]; luteal or luteal-like interstitial cells [Kirschbaum & Frantz (21)] are probably the sources of androgenic secretion.

Gonadotropically-induced changes in the connective tissue of the rat ovary, revealed by the periodic acid-leucofuchsin reaction, indicate a process of depolymerization of mucopolysaccharides (22). Such changes would allow structural rearrangements within the ovary, which may be mediated by enzymes of the mucinase class [Catchpole (4)].

Claesson *et al.* (23) found no appreciable increase in estrogen production in the interstitial glands at parturition or during lactation. In the interstitial gland and corpora lutea (24) of the pregnant rabbit, the ascorbic acid levels are markedly depressed within three hours after PMS injection. Later, they rise to higher than prestimulated levels.

In young corpora lutea in the mouse ovary (25), histochemically-revealed lipase is heavily concentrated. In the rat corpora lutea of pregnancy, glycolytic activity remains unchanged until the twentieth day and then drops until the fourth day of lactation (26); a mitotic activity disappears by the fifth day and a late phase at about the twelfth to fifteenth day.

Reaffirmations of the thesis that massive doses of stilbestrol exert a direct effect on the ovary have been presented by Desclin (27) and Robertson (28). However, Iglesias *et al.* (29) have reported that estradiol pellets, transplanted with the ovary into the spleen of the castrated guinea pig, do not exert sufficient local action to prevent the formation of hemorrhagic follicles; and as little as 1.8 μ g. per day adsorbed from subcutaneous pellets, acting presumably via the hypophysis, protected similarly transplanted ovaries from forming hemorrhagic follicles (30). Other observed effects of stilbestrol show an inhibition of the goitrogenic action of antithyroid drugs in the rat (31), an increase of lipid concentrations in chick tissues (32), a raised adrenal weight, but lowered ascorbic acid content in the guinea pig (33), and a lowered adrenal weight and carbonyl lipid in the hamster (34).

In the rat, ovarian sensitivity to gonadotropin is elevated by propyl thiouracil (35) and depressed by thyroxin (36), which effect is in some way counteracted by administering liver residue (37). Stein & Foreman (38) report a proliferation of cells of the germinal epithelium caused by thyroid substances in contrast to an inhibiting effect produced by thyroxin. Prostig-

mine was observed by Blaylock & Emery (39) to produce a slight increase in uterine weight. A stimulating effect of FSH on the oxygen consumption of chick ovary slices is claimed by the Nalbandovs (40). Meyer & McShan (41) have reviewed earlier work of the Wisconsin laboratory on the hormonal control of ovarian enzymes.

The uterus, fallopian tube, and mammary gland.—Hall (42) observes that daily vaginal smears in the rat lessens the induction of pregnancy and pseudo-pregnancy. Salvatore (43) suggests that the cells of uterine reconstruction after puerperium are not cells of the pregnant period which reduce in size after labor, but are cells which arise by the mitosis of those that grew during gestation.

Several recent studies have appeared on the hormone-induced changes in the alkaline phosphatase content of the female reproductive tract, and the results largely confirm previous work; Atkinson (44) has reviewed the earlier investigations on the endometrium, and Ring (45) has followed the alkaline phosphatase changes during the estrous cycle of the rat in the uterus, cervix, and the vagina. In all of these sites, there is a maximal enzymatic activity during proestrus and early estrus. Ring suggests a relationship between alkaline phosphatase content and vaginal keratinization. As in the rat, the estrogen-elevated endometrial phosphatase activity in the guinea pig is counteracted by both progesterone and testosterone (46). Andrus *et al.* (47) find that estrogen-induced elevation of alkaline phosphatase in the chick oviduct requires the presence of pteroylglutamic (folic) acid. Other pertinent observations have been reported. During the normal menstrual cycle, hyaluronidase concentration in blood serum is highest during menstruation, and no significant change occurs during pregnancy and labor [Hakanson & Glick (48)]. Acetylcholine, however, gradually appears toward the second trimester of pregnancy, increases with the onset of labor, and disappears within 48 hr. after labor [Chang, *et al.* (49)]. The iron content was studied as a quantitative measurement of the effect of previous pregnancies on the mammary glands of mice by Rawlinson & Pierce (50).

Peckham & Greene have studied the failure of decidual formation in the rat after the first week of pregnancy and find that the failure is not attributable to progesterone deficiency but rather to the presence of an inhibitor, probably estrogen (51). Removal of both the ovaries and the products of conception restores decidual formation, and the daily administration of 1 μ g. estrone suppresses it. Chambon (52), also, has inhibited decidual formation in the rabbit with estrogen.

Testes, epididymides and seminal vesicles.—Employing histochemical methods, Wislocki (53) observed that steroid hormones are produced in the interstitial tissue. By means of polarized light, Kumaran & Turner (54) detected precursors of male sex hormones in the interstitial tissue and saw what may be considered storage pockets. In autogenous grafts of the testis [Williams (55)], the Sertoli cells are stimulated by LH to form droplets, interpreted as secretion. McEnery & Nelson (56) demonstrated sudanophilic

lipid in the Leydig cells and basal areas of seminiferous tubules of all species studied. Taber (57) finds that the interstitial cells are the main source of androgen in the male chick; Nelson (58) found no water soluble inhibin.

Perlman (59, 60) has discussed the functional significance of testis cholesterol. He finds it more concentrated in the seminiferous tubules than in interstitial cells, and it may be more significant in the spermatogenic process than in androgen production (60). The administration of cholesterol does not decrease the effective dose of sex hormone [Bacon (61)]. Tepperman *et al.* (62) find that with the use of purified gonadotropins, the increase in rat testicular cholesterol esters is under the control of LH rather than FSH as previously suggested.

Low dosages of testosterone may injure the testis by suppressing secretion of gonadotropin, while higher doses of the androgen are adequate to stimulate directly seminiferous tubules [Ludwig (63)]. Kumaran & Turner (64) find that FSH causes degeneration of primary and secondary spermatocytes and in older birds increases the growth of spermatids. In hypogonadism, Hurxthal *et al.* (65) report that testosterone alone and LH alone promote spermatogenesis. Baker *et al.* (66) report that adrenocorticotrophic hormone (ACTH) produces atrophy of the testicular Leydig cells and involution of seminal vesicles, but does not affect spermatogenesis. Treatment with testosterone propionate increased the hyaluronidase content in the testes of the rat which may be caused by the increased number of cells according to Riisfeldt (67). In immature pigeons, progesterone increases testicular weight, possibly by stimulating the release of greater output of interstitial cell stimulating hormone (ICSH) and FSH from the hypophysis [Kar (68)]. Kumaran & Turner (69) observed that mild hyperthyroidism in birds stimulates the final stages of spermatogenesis. Pregnenolone has no effect on spermatogenesis in hypophysectomized rats [Dvoskin (70)]. The newly available pure FSH [Li (71)] activates spermatogenesis in the hypophysectomized rat without stimulating interstitial cells [Simpson *et al.* (72)]. Rossen-Runge (73) describes waves of divisions of spermatogonia with about five to six divisions occurring per wave.

The alkaline phosphatase content of the male genital tract has also received some attention. Bern (74) has presented a comparative study of seven mammals; Stafford *et al.* (75) have shown that testosterone elevates and castration depresses both alkaline and acid phosphatase in the rat seminal vesicles and prostate. Leblond *et al.* (76) have demonstrated polysaccharides in the head cap of developing spermatozoa with the use of the periodic acid-leucofuchsin technique. Humphrey & Mann (492) have studied the citric acid in semen.

Cytochemical reactions of human spermatozoa have been studied by Wislocki (77), and morphological studies have been conducted by a number of investigators. Reporting on the frequency of beat of sperm tails, Ritchie (78) finds the lowest rate to be 14 to 16, the highest 25 to 28, which is the same rate as cilia or flagella of clam gills; bursts of activity were observed.

Emik & Sidwell (79) observe most frequently tailless ram sperm distal to the ampulla. Autoradiographs of bull sperm show that the posterior part of the head and midregion accumulate isotope P^{32} [Bishop (80)]. Triphenyl-tetrazolium chloride is not suitable as a vital stain for bull sperm or as a means of measuring their viability [Mixner (81)].

Wallace (82) reports that, in the castrated boar, a brief treatment with stilbestrol has no effect on semen production, which was decreased after long term treatment. Huston & Wheeler (83) find that synthetic thyro-protein reduces the amount of cock seminal fluid, but not sperm production or fertilizing capacity.

Seminal hyaluronidase is formed from the galea capitis, but investigations by Dalgaard-Mikkelsen (84) that it promotes fertility were not conclusive. The turbidometric method of assay by Mixner & Johnston (85) suggests the possibility of expressing potencies in terms of a standardized unit. Johnston *et al.* (86) obtained only negative partial correlation of initial hyaluronidase with initial percentage of live sperm and with the percentage of live sperm surviving cold shock. Some relationship between sperm count and hyaluronidase in infertile marriages was observed by Michelson *et al.* (87), and Riisfeldt (88). Preparations of bull hyaluronidase are stable at 10°C. and at room temperature for over a year [McCullagh *et al.* (89)]. The anti-hyaluronidase activity of phenol substitution products increases with the length of the carbonic side chains [Calesnick & Beutner *et al.* (90)]. Following maximal concentration injections, hyaluronidase disappears from the blood of rats within one hour, and two per cent appears in the urine [Elster & Lowry (91)].

Lovelace (92) observed the effects of precocious sperm entry on the egg of *Nereis limbata*. Several investigators have studied the efficacy of various semen diluters in relation to motility and fertility of sperm. Pursley *et al.* (93, 94) increased the viability of sperm 2.5 times by hypo- and hypertonic solutions and egg yolk citrate; Cheng *et al.* (95) observed a decrease in motility with high dilutions, but no correlation between motility and fertility; Gilbreath & Davis (96) found a positive correlation between concentration and fertility in the turkey, and Willett (97) and Bratton *et al.* (98) noted a decrease in motility with high dilutions. Dunn *et al.* (99, 100) report that whole egg extenders are as satisfactory as egg yolk and cost about one-fourth as much; fertility is about the same. Synthetic pabulum is 15 per cent less satisfactory [Bayley *et al.* (101)] than yolk citrated. The fertility level of semen is increased by the addition of a citrate sulfanilamide yolk extender before cooling to 5° C. [Foote & Bratton (102)] which effect can not be accounted for by the difference in the number of motile sperm. Cooling to about 0°C. increases the longevity of bull sperm [Gonzaga (103), Stone *et al.* (104)]. From data on respiratory metabolism, Ghosh *et al.* (105) were unable to foretell the fertilizing ability of bull sperm. Tepperman *et al.* (106) studied the metabolism of rat testis in vitro. Bacteriological studies of bovine semen by Prince, Almquist & Reid (107, 108) reveal no apparent relation between the

number of bacteria in semen and its fertility potentialities. Spikes (109) presents further evidence that the reactions between the specifically combining substances of eggs and sperm are similar to serological reactions. Mann (110) has published a review on the metabolism of sperm.

NERVOUS AND HORMONAL FACTORS CONTROLLING THE PITUITARY-GONAD AXIS

The basic concepts of nervous involvement in pituitary-ovarian relationships have been reviewed by Everett (111), and the application of these concepts to the human menstrual cycle were reviewed by Bowman & Reifstein (112). The new observations have strengthened the position of the hypophyseal portal veins as the route by which the nervous system exerts its control over the adenohypophysis. Green & Harris (113) observed in the living rat and frog that the flow is from median eminence to pars distalis. Even more significant is Harris' report (114) that after pituitary-stalk-section in the female rat, the return of normal sex function is closely correlated with regeneration of the portal vessels beginning as soon as 24 to 48 hr. after section. This discovery provides an explanation for earlier claims of unimpaired nervous-hypophyseal function after stalk section. Drager (115) describes neurosecretion granules which pass from the hypothalamus towards the hypophysis. A counter report of direct nerve fibers passing along the stalk to the gland cells in the rabbit has been published by Vazquez-Lopez (116). Unfortunately, the silver technique admittedly stains reticulum, and several of his animals had encephalitis. In *Amblystoma*, Blount (117) transplanted the hypophysis alone and also, with the floor of the diencephalon; in the latter he found an increase in hormone production. Earlier physiological results [Markee *et al.* (118)], confirmed by Harris (119), that the adenohypophysis is electrically inexcitable favor the vascular over the nervous route as the final pathway in neurogenic control of gonadotropin release.

This laboratory has developed a concept of neurohumoral control of the release of ovulating hormone (LH or total gonadotropin) which involves cholinergic and adrenergic components in sequential arrangement. Our scheme was based on the findings in the rabbit that intrahypophyseal epinephrine, but not acetylcholine, induced ovulation (120), that copulation-induced ovulation could be blocked by injecting the antiadrenergic agent Dibenamine within a minute post coitum (121), and that even more rapid injections of the anticholinergic agent, atropine, would also block stimulus for LH release (122). The results suggested that a cholinergic mechanism might stimulate the release of an adrenergic mediator which in turn would activate the adenohypophysis. Failure of systemic injections of epinephrine to induce ovulation differentiated this mechanism from that controlling ACTH release (123) and argued for local production of the adrenergic mediator in the sequence leading to LH release. We have demonstrated that the ability of Dibenamine to block ovulation is not due to its ability to stimulate the central nervous system (124) and that SKF-501, a more potent adrener-

gic blocking analogue of Dibenamine, blocks the stimulus for LH release with a minimal central excitatory effect (125). The adrenergic mediator is probably not epinephrine itself, since the imidazoline derivative C-7337 exerts rapid antiepinephrine effects without blocking the copulation-ovulation reflex. Atropine exerts considerable protection against epinephrine by blocking pulmonary edema. It does not, however, prevent ovulation by adrenergic blocking properties, for in the atropinized rabbit, otherwise lethal dosages of epinephrine have been found to activate LH-release (126).

Kehl & Molina (127, 128) have reported that, in the rabbit, the injection of procaine directly into the hypothalamico-hypophyseal region prevents the ovulatory effect of serum and chorionic gonadotropins, as was reported previously by Westman & Jacobsohn (129). These results cannot indicate blockade since chorionic gonadotropin does induce ovulation in the absence of both the hypothalamus and the hypophysis (130).

The chemical stimulants of LH release, picrotoxin and copper salts, apparently function by differential mechanisms; picrotoxin exerts its effect via the nervous system, whereas copper stimulates adeno-hypophyseal cells directly (131, 132). Evidence for the above is that the copper stimulus succeeds in spite of nervous-blocking agents and that very weak dosages of copper acetate injected directly into the anterior lobe induce ovulation.

Evidence obtained in the rat (133, 134) indicates that, even in the so-called "spontaneously" ovulating species, the stimulus for LH release is controlled by nervous mechanisms employing cholinergic and adrenergic components. Ovulations which would be accelerated one day by progesterone can be delayed one day by atropine or Dibenamine—the period of sensitivity is almost exactly 24 hr. earlier than normal and is evidence of a 24-hr. rhythm in some element of the LH-release apparatus (135). Striking confirmation of this concept of a 24-hr. periodicity has been found in the fact that sedation with barbiturates during the critical hours of proestrus will prevent ovulatory activation of the hypophysis (136, 137). If barbiturate sedation is repeated on successive afternoons at the same critical hours, the graafian follicles persist for two to three days. Other features of the estrus cycle do not, however, remain static, and an experimental dissociation between ovulation and uterine and vaginal cycles results (138).

Jacobson *et al.* (139) have reported that the induction of pseudopregnancy by electrical stimuli in the rat is blocked by epinephrine or acetylcholine as readily as by their specific antagonists. However, epinephrine-induced resistance to further epinephrine [Sawyer *et al.* (126), Last *et al.* (140)] indicates that this agent may act on occasion as an adrenergic blocking agent.

The year has brought much confirmatory evidence of the stimulatory action of progesterone on the LH-release mechanism, Kempf (141) has reported that progesterone stimulates ovulation in ovaries implanted into the ears of castrate male rats. Neher & Fraps (142) employed progesterone in chicks to force ovulation of additional eggs to a clutch. Pfeiffer (143) has reported ovulation in monkeys during their anovulatory summer cycles by proges-

terone treatment. Sawyer (144) induced ovulation in the estrogen-treated rabbit by mechanical stimulation of the vagina and by combined treatment with estrogen and progesterone (145).

FEMALE INTERRELATIONSHIPS

Estrogen.—Jailer (146) has published a review on the metabolism of estrogens. The estrogen level has been determined in the nonovulating rabbit (147), in the blood of the ovarian vein of the dog and spermatic vein of the stallion (148) where it is 5/14 higher than in the systemic veins, in the urine during human menstrual cycles and during pregnancy (149), in the human after massive dosages of estrogen (150), in the urine of the pregnant mare (151), and in the tissues after an interval of 13 weeks after administration of estrogen (152). It occurs in grass in amounts sufficient to increase the uterine weight of test mice and milk production in cows (153). The variations in estrogen blood level are accompanied by changes in the serum level of choline in women during the menstrual cycle (154).

Estrogen is antagonized by Δ^5 -pregnenolone (155) and by progesterone (156); the two have different effects on *Plalypocilus maculatus* (157). Estrogen induces mating in spayed adrenalectomized rats (158). When given with progesterone, it induces endometrial hyperplasia in diabetics (159), but it causes an inconstant luteinizing reaction in ovaries of normal individuals (160). It produces changes in the human vaginal smear in the following order of effectiveness; stilbestrol, estrone, estriol (161).

Progesterone.—Guterman (162) has published a review on the physiologic basis for clinical applications of progesterone. Although Hooker & Forbes (493), using a biological assay, reported 4 to 8 μ g. per cc. in mice, rabbits, monkeys, in pregnant women and during the menstrual cycle, and [Fraps *et al.* (163)] in the plasma of cocks and nonovulating hens, Haskins (164) failed to reveal the presence of progesterone in the blood plasma of pregnant women by ultraviolet absorption studies. Henderson *et al.* (165) published a review on pregnenolone.

Zarrow *et al.* (166) find that desoxycorticosterone is converted into progesterone, and Guterman (167) studied the conversion of progesterone into pregnanediol. Huber (168) reports that progesterone activates the uterus and Krantz (169), that it makes the uterus relax after priming with estrogen. It is absorbed percutaneously (170). Bradbury (171) has studied its ability to maintain uterine growth instituted by estrogen.

Hooker (172) has investigated the reduction of plasma progesterone levels and presents figures which may be calculated to demonstrate that 864 mg. is either secreted or reactivated per day. If these figures are compared with Haskins' inability to demonstrate progesterone by ultraviolet absorption studies (164), it becomes obvious that further quantitative determinations are indicated.

Relaxin.—Frieden & Hisaw (173) have extracted a relaxin from pregnant sow ovaries with a purification of 500 to 1,000-fold. Zarrow (174, 175) finds

that relaxin causes water retention in the rabbit and an anemia comparable to that which occurs in the last third of pregnancy. Relaxation of the pelvic ligaments was produced by prostigmine and acetylcholine in guinea pigs primed with estrogen (176), but relaxation was not produced by progesterone in the mouse although a high estrogen-progesterone ratio near term may be effective (177).

Estrous cycles.—In the rat, estrous cycles were unaffected by daily injections of prostigmine, indicating that systemic administration of this anticholinergic agent fails to stimulate the hypophysis (41). Plant extracts of *Lithospermum rudervale* inhibit estrus in the rat without blocking vaginal cornification following estradiol administration (178). Drasher (179) suggests that the *Lithospermum* inhibits LH production, but inhibited release of LH would be equally attractive. The threshold for cervical stimulation of pseudopregnancy in the rat has been reported to be raised by taking daily vaginal smears (42).

Neurosecretion granules, thought to contain chemical mediators for the control of hypophyseal secretion, have been reported in the supraoptic nuclei and pituitary stalks of cats and dogs (180) and in the tropical indigo snake. The intact hypophysis and tuber show an increased P^{32} turnover in response to estradiol (181). That the tuber itself does not produce gonadotropic hormones is evidenced by the work of Westphal (182). Psychic estrus in the hamster was induced by desoxycorticosterone [Isaacson (183)] or by progesterone administered by the lateral brain ventricle [Kent & Liberman (184)]. Withdrawal and hormone induced changes in uterus and vagina were described [Kent & Roberts (185)] as well as those during pseudopregnancy.

Changes occurring during the estrous cycle have been described for dairy cattle [Asdell *et al.* (186)], the North American rodent, the pika [Duke (187)], and for the Ca'aing whale [Harrison (188)]. Several types of false corpora lutea have been produced experimentally in the rat [Bourg (189)], and accessory ones have been found in the Canadian porcupine [Mossman & Judas (190)]. Although the steroids, estradiol, progesterone, and desoxycorticosterone increase the water content of the uterus, etc. (191), there is a significant decrease in the water content of the rat uterus during estrus.

Menstruation.—The recent main theories of the mechanism of menstrual bleeding have been presented in a book, *Menstruation and Its Disorders*, edited by Engle (192). Markee (193) presents some additional evidence for rapid local regression as the cause of bleeding and the relation of the coiled arteries to the regression. Okkels (194) presents the evidence for arteriovenous shunts [see also Schlegel (195)]. The moot question is whether the necrosis that they and Markee agree on is due to activity of the shunts or of the coiled arteries. The Smiths (196, 197) present their evidence for the role played by menstrual toxin. The important question is whether menstrual toxin causes the necrosis [Smith (197)] or results from necrosis [Markee (193)].

Zuckerman (198) has presented some new evidence on the neural factors

in the menstrual cycle, i.e., transection of the spinal cord produces menstrual bleeding, apparently, through vascular shock. Forbes (199) finds some progesterone before ovulation and a peak several days after ovulation ($5.2 \mu\text{g}$. per cc.), with a marked decrease usually preceding menses. Menstrual bleeding occurs during the continuous administration of estrogen (200), after the withdrawal of various estrogens (201), progesterone (202), gonadotropin (203) and androgen in the postmenopausal woman (204). Prostigmin does not induce menses in the monkey [Kaiser (205)].

Amenorrheas may be of four types (206), and there may be a psychosomatic factor (207). Intermenstrual bleeding may be due to a fall in estrogen (208), and it can be correlated with the "ovulatory temperature shift" (209). Menstrual disturbances may be due to hormonal imbalance (210) and to neuro-hypophyseal disorders (211). They can be treated by oral hormone therapy (212), x-ray (213), stilbestrol (214), and estrogen (215). The vagina reacts to a smaller amount of stimulant than the uterus [Zondek *et al.* (216)]. Pain from endometriosis may be due to action of menstrual toxin on the nervous system (217). Endometrial hyperplasia results from continued stimulation by estrogens or FSH (218). Progesterone withdrawal causes a type of menstruation which cleans the endometrium of its superficial layers (219). This effect may result from the additional growth induced by progesterone. The mucous membrane of the isthmus is a continuation of the basalis [Danforth & Chapman (220)]. The ectopic endometrium of endometriosis is of an immature type which reacts to estrogen but not to progesterone [Novak & de Lima (221)]. Accessory changes occur in the number of circulating eosinophils during the menstrual cycle (222) and in the basal metabolic rate which fell sharply at the age of 46 in one woman (223). High protamine levels occur during the menses, especially in patients with menorrhagia (224), and the amount of serum which may be extracted from the clot decreases during the first week of the menstrual cycle (225). Estrogen is not retained by the cervix in high enough concentrations to cause carcinoma, as is evidenced by the low incidence of endometrial hyperplasia in patients with cervical carcinoma (226).

Glycogen.—Mapleson (227) used a modified Best's carmine technique for staining glycogen in vaginal smears. Ayre & Ayre (228) have studied vaginal smear glycogen and estrogen activity. Gestational and cyclical variations occur in glycogen and in reducing substances in vaginal mucus (229). Hughes *et al.* (230) investigated the presence of glycogen in sterility and habitual abortion. Lipphardt & Pommerenke (231) studied the effect of spermatozoa on the sugar content of cervical mucus. Atkinson *et al.* (232) found that the amount of mucus liberated by the human cervix is increased at mid cycle and during pregnancy.

Ovogenesis.—There have been a number of studies on the development of egg cells from the germinal epithelium. The primordial germ cells persist for nine days in the rat (233); they are not formed from the germinal epithelium after the fifteenth day in the rat (234) but do develop from this source even

in the adult human (235, 236). The number of mature follicles in the immature hamster is increased by FSH (237) which may be prepared from sheep or hog pituitaries (238). The layers of the envelope are influenced by the activity of the ovum and oviduct (239). The grasshopper egg (240) and embryonic avian tissue (241) have been studied by electron microscopy.

Ovulation, insemination, fertilization, and fertility.—Ovulation depends upon the balance between FSH and LH (242) and has been induced by gonadotropin in the sow (243), the ewe (244), and the goat (245) as has superovulation in cattle (246) and mice (247). The time of ovulation is reported during normal menstrual cycles (248) and during lactation (249). The validity of the Farris test for ovulation has been investigated (250). Ovarian autographs have been studied in the eye of a monkey (251) and in the spleen of mice (252). The neurohumoral control of ovulation was treated on preceding pages. Other pertinent investigations deal with hypophyseal comb relations (253), gonadotropin level in the absence of ovaries (254), and the effects of estrogen on young and old monkeys (255), and on rats (256).

Further studies on insemination in amphibia (257) and *Drosophila gibberosa* (258) have been reported, indicating an unidentified active substance in the semen. The vagina of the rabbit has a unidirectional permeability (259). The site of fertilization has been studied in the rabbit, the rat (260), and the hedgehog (261). Substances associated with fertilization have been investigated (262, 263).

Asdell (264, 265) reviewed nutrition and the treatment of sterility in cattle. Other reviews in the field of fertility and sterility were published by Sykes (266) and Gilmore (267). There are additional papers on fertility in the human (268, 269, 270), rat (271, 272), swine (273, 274), horse (275), and cow (276) and on the effect of altitude on fertility in the rat (277). There have been studies on intersexuality (278) and on a case of possible superfetation in the mouse (279). In precocious sexual development, the dental and nervous tissues seem least responsive to hormonal stimulation (280).

Uterine contraction.—The second edition of the *Physiology of the Uterus* by Reynolds (281) covers all but the most recent references on uterine contraction. There have been studies of the influence on uterine activity of epinephrine (282, 283), morphine (284), actomyosin (285, 286), and adenosine-triphosphatase (287), and of drug responses (288), diffuse uterine enlargement (289), clinical experiences with myometrial activity (290), a comparison of the motility of the uterus and oviduct (291), and the preparation of the uterus for labor by the Braxton Hicks contractions (292).

Pregnancy and toxemia of pregnancy.—Mussey (293) published a review on reproduction which deals especially with the nutritive requirements during pregnancy and lactation. Diethylstilbestrol may prevent diabetes in force-fed rats [Rodriguez (294)], but stilbestrol does not prolong pregnancy (295). Pregnancy occurred in alloxan diabetic rats not given insulin [Levi &

Weinberg (296)]. Diethylstilbestrol [Bertling & Burwell (297)] and drama-mine [Carliner *et al.* (298)] relieved the nausea and vomiting of pregnancy. Plasma volume increases 40 per cent [McLennan (299)] and diminishes during the last month of pregnancy; meanwhile, the erythrocytes show a greater range in size [Merivale & Richardson (300)]. The postpartum vascular changes resemble those due to closure of an arteriovenous shunt [Sampson (301)].

A symposium on the toxemias of pregnancy was sponsored by the Ciba Foundation in January, 1950 (302). The frequency of eclampsia during the war years was reported for Budapest (303), Amsterdam (304), and Finland (305), and the importance of lack of fresh air (303), nutritional deficiency (304), and salt and fat (305) were discussed. Brust *et al.* (306) report that the blood pressure floor is elevated by humoral tone, and Assali (307) finds that 933F is of no value. McCall (308) found an increased cerebral vascular resistance and lowered oxygen consumption in eclampsia, but not in normal pregnancy. Péteri & Tarján (309) report that during eclampsia the blood contained a substance which has a depressor effect on cats. Austin & Frymire (310) find that an original hypertension may be aggravated during pregnancy. Loeb *et al.* (311) state that the rat is more susceptible to renal damage during pregnancy; and Dieckmann *et al.* (312) report that elimination of water is delayed, especially during pre-eclampsia.

The spontaneous rupture of the vaginal closure membrane during the second trimester in the guinea pig may be due to a shift in the control of the hormonal balance from the ovary to the placenta (313). At a comparable time in the human, diminished vascular growth could produce premature uterine ischemia (314). Reynolds (315) has studied other factors which are related to ischemia of the placenta. Thromboplastin may be the chief activator arising from placental damage (316). Rutin reduced capillary fragility, which is increased during pregnancy (317).

Pregnancy may place a work load on the mother (318), the toxemia may be a so-called "Selye disease of adaptation" (319), and the excretion of corticosteroids is elevated during pregnancy. Pregnenediol elimination decreases during eclampsia (320), histidase is reduced (321), but there is no change in the histamine content of the plasma or urine during parturition. The uric acid clearance is disproportionately depressed (322).

Intrauterine death.—Potter & Adair (323) have written a book on *Fetal and Neonatal Death*. Death during development results from a number of causes: vitamin A deficiency (324), anomalies of the later stages of development of the follicle (325), and an ovicidal factor (326). The prenatal mortality is higher in female than in male chicks (327). The prenatal mortality in mammals and the ratio of corpora lutea to the young have been studied in the wild rat (328).

Fetal and neonatal absorption.—Many substances readily pass through the placenta, such as vitamin E (329, 330) which protects the placenta from vascular changes (331), iodine¹³¹ (332), iron (333), propylthiouracil, and thy-

roxine, but not thyrotropin (334), maternal plasma (335), and vitamin A (336). Curare is blocked by the placenta (337). There is a positive correlation between the nutrition of the mother and fetus (338). Fructose may be formed by glycogen breakdown in the fetus (339). The characteristics of colostrum have been studied (340); proteins in the colostrum appear as new proteins in the blood of the young (341).

Mammary gland.—Lobulo-alveolar growth is induced by gonadotropin through ovarian luteinization (342), and duct growth is induced by the nine estrogens studied (343). Combinations of estrogen and progesterone are most effective (344). Growth of the mammae is not influenced by adrenalectomy (345). Differentiation progresses similarly in the two sexes for the first year (346, 347); atrophy occurs during the fourth decade and renewed growth in the fifth decade. In the cow, the parenchyma shows a lamellar structure (348), and between 3 and 30 months, the capacity of the udder increases 0.44 lb. per month (349). Inhibition of the development of and a decrease in the number of mammary glands in mice follows the administration of androgens during development (350). Age is a second factor inhibiting the stimulating effect of estrogen on mammae (351).

Lactation.—The chemistry and physiology of prolactin has been reviewed by White (352). Lactation is induced by the removal of luteinized ovaries (342) or administration of prolactin during pregnancy or pseudopregnancy in the rabbit; it continues at a reduced level for three weeks after transection of the hypophyseal stalk (353); and it can be initiated by estradiol after this operation (355). Folley (354) has described a neurohumoral mechanism for the control of the discharge of milk from the mammary gland.

The concentration of various constituents in the blood of dairy cows during lactation has been studied by Latschar *et al.* (356) and compared with human milk by Block & Bolling (357). The composition of the milk is influenced by a number of factors: in cows, increase in body temperature increases the solids-not-fat and the milk yield (358); the milk yield and fat are also increased by thyroprotein in the daily ration for one to two months (359); the vitamin A content and calcium are increased by an interruption of milking (360). A new equation has been established for calculating the solids-not-fat from the fat content of cows' milk (361).

Destruction of hormones and inhibition by pteroylglutamic acid.—All but 5.8 per cent of human gonadotropin is inactivated or destroyed in the post-partum period (362), presumably by the liver (363) which also inactivates estrogen on high but not on low protein diet (364). In the guinea pig, carbon tetrachloride increases the estrogen excretion 350 times (365) and the liver inactivates androgen even after extensive destruction of the liver (366). However, monkey liver does not inactivate estrogen (367), and immature rat liver does so only incompletely (368). The above raises the question of whether the human liver inactivates estrogen, as is indicated by the high incidence of carcinomas in Africans with extensive liver damage (369).

Basic estrogen production is only about 1.8 μ g. per day (370). The renal

threshold for chorionic gonadotropin remains constant during pregnancy (371). Implanted endocrine tissue provokes an organ specific immunological reaction (372). Pteroylglutamic acid inhibits the effect of estrogen, but not of androgen, on the prostate (373, 374). Ely *et al.* (375) investigated the progonadotropic property of dilute antigonadotropic serum. Østergaard & Hamburger (376) detected the formation of antihormones in women treated with pregnant mare serum (PMS) hormone.

MALE INTERRELATIONSHIPS

Male sex hormone.—The metabolism of androgen has been widely studied, including its effect on tissue respiration and its anabolic activity (377), which is greater in the male than in the female rat (378). The response to androgen is governed by an adequate food intake (379), and the resistance to starvation is greater in rats receiving androgen (380). Its activity may be tested by applying it directly to the chick's comb (381). DDT retards testes growth, perhaps because of an estrogen-like action (382). There have been studies of androgen excretion, such as its metabolic products in the urine (383), its metabolism in a hypogonadal man (384), its derivatives in metastatic cancer (385), and its excretion in cows with adrenal virilism (386).

Mating behavior.—In the female, psychic or vaginal estrus occurs in the hamster after partial ovariectomy (387) and the administration of desoxycorticosterone (183). Spayed, adrenalectomized rats mate after rapid administration of large doses of estradiol (388), but these facts do not mitigate the role of progesterone in normal mating.

In the male, androgens increase mating behavior in the hamster (389), rabbit (390), and human (391); although libido and potency may be normal despite diminution or absence of gonadal substances (392). In the human, impotence must be considered from the psychiatric standpoint (393), and if due to active vasoconstriction, it might be relieved by infiltration of the lumbar sympathetic chain (394). Androgen may increase sex drive, partly by stimulating the tactile functions of the glans penis (395). Androgen combined with somatotropin induces maximum growth of the os penis of the rat (396). Guinea pigs with high and low sex drive have different patterns of sex behavior which are at least similar to two patterns of sex behavior in the human (397). In guinea pigs, the amount of thyroxine which reduces body weight 10 to 15 per cent in a month does not reduce sex drive (398). In male rats, the increased sex behavior at night may be due to a higher metabolic rate (399).

Sex hormone assays.—Some of the recent bioassays warrant special comment. Deming & Luetscher (400) describe a test for desoxycorticosterone with a sensitivity of 10 $\mu\text{g.}$; Hooker & Forbes (401) report that their intrauterine test for progesterone (only 0.0002 $\mu\text{g.}$) is negative against 23 related substances; Emmens (402) states that the intravaginal assay of naturally occurring estrogens can be repeated without priming the mice. Ladman & Jackson (403) find that the pregnant mouse is eight times as sensi-

tive as the immature mouse for the assay of unfractionated pituitary glands; Smith & Gardner (404) used uterine weight as assay for pituitary gonadotropin; and Lloyd *et al.* (405) have used uterine weight and ovarian hyperemia as a test for urinary gonadotropins. Eichenberger (406) describes a fluoroscopic method for the determination of estrone, estradiol, and estriol in pregnancy urine, which is sufficiently sensitive for diagnosis of pathological changes. Loraine (407) published curves for the urinary level of chorionic gonadotropin during pregnancy. In spite of the often reported decrease in gonadotropin, the errors in pregnancy tests are not reported to increase as the amount of chorionic gonadotropin decreases.

Pregnancy tests.—Three types of pregnancy tests have been widely reported. (a) The liberation of sperm by the male frog or toad about three hours after the injection of 5 to 10 ml. of human pregnancy urine or blood plasma from pregnant mares into the dorsal lymph sac, gave quite good results (408 to 419). The factors influencing this reaction have been investigated (420 to 423), and the response seems to be due to FSH (420). (b) The quantitative determination of pregnanediol is about 90 per cent accurate as a rapid test for pregnancy (424, 425). (c) The reactions in the rat and mouse ovary as tests for pregnancy are still being investigated (426, 427). Ovarian hyperemia seems to be due to LH, and the response is increased by the addition of FSH (426). Ovulation in the pregnant mouse may be induced by one-eighth the amount of gonadotropin required by the post-parturitional mouse (428).

Perhaps even further increase in the sensitivity of pregnancy tests and biological assays of gonadotropins may be anticipated. Two additional types of tests have been reported. Pregnancy may be diagnosed on the bases of (a) the secretion obtained from the cervix of a pregnant mare (429) or from the changes in the type of exfoliated human cervical cells (430), and (b) the response of melanophores in *Rana esculenta* to a melanophore expanding hormone, which is apparently produced in greater amounts during pregnancy, supposedly through stimulation by progesterone.

Pregnanediol.—Hoyt & Levine (431) report an improved procedure for the quantitative estimation of urinary pregnanediol. It is inhibited by carinamide [Bissell *et al.* (432)], but is not influenced by vitamin E [Jones *et al.* (433)]. The butyl alcohol and acetone fractions run parallel during pregnancy but are different in ovulatory and anovulatory cycles (434). It is high in the postovulatory period (435), but it is not definitely related to the so-called ovulatory change in temperature [Rogers & Sturgis (436)]. It is excreted in small amounts by the "denervated" spleen grafted ovary (437). Smith & Schiller (438) and Davis & Fugo (439) have investigated the difference in opinion as to whether stilbestrol injected into a pregnant woman increases pregnanediol elimination as measured by the Venning and by the colorimetric assays.

Thyroid relationships.—The morphogenesis of the thyroid and iodine accumulation have been studied in the calf (440). The absence of the thyroid is

compatible with normal pregnancy in the guinea pig (441), as is thyrotoxicosis in the human (442). Small amounts of estrogen increase and large amounts decrease iodine turnover (443); the latter may be the cause of the presence of thyrotropin in the blood of pregnant women (444). The destruction of the thyroid by iodine 131 stops ovogenesis (445), but throxine decreases the ovarian response to gonadotropins (446), and luteinization is more easily induced in hypothyroid rats (447).

Local action and modes of administering hormones.—Follicular growth is not due to the local action of estrogen (448), but is induced by local action of gonadotropin. Androgen crystals implanted near seminal vesicles act locally (449), as does an ovarian transplant near a seminal vesicle (450). The mode of administering a hormone (451 to 456) and the medium (457, 458, 459) affect its absorption. Bates & Lowry (460) find that particle size is of primary importance in controlling the duration of effectiveness of estrogen.

Influence of sex steroids on enzymes outside of the genital tract.—The thesis that hormonal effects are generally evoked by a fundamental action on enzyme systems has also stimulated further investigations of hormone-enzyme relationships at other sites. Alkaline phosphatase lost from the duodenum and jejunum in response to castration, is restored by a variety of sex steroids (461). Estrogen increases the content of the enzyme in the proximal convoluted tubules of the rat kidney (462) and reduces the enzymic activity in the pigeon adrenal cortex (463). Testosterone increased the cytoplasmic alkaline phosphatase of the mouse thyroid (464) as well as the phosphatase and mucopolysaccharide content of the cockerel's comb (465). Estradiol inhibits the latter, probably by suppressing gonadotropic secretion by the adenohypophysis (466). Indeed, one must always consider the possibility that the influence of sex steroids on enzyme synthesis is pituitary-mediated. In the submaxillary of the mouse, protease and probably the phosphatase of the serous tubules show a sexual dimorphism, which is more prominent in the male (467). Grad & Leblond (468) have shown that the maintenance of the serous tubules requires the synergistic action of testosterone and thyroxine. Kochakian (469) has reviewed the effects of androgens on enzymes of the liver and kidney. Both androgens and estrogens have been reported to inhibit the *in vitro* oxygen uptake of rat liver, kidney, and brain slices (470). Castration decreases the sensitivity of tissue slices to the oxidative-inhibiting action of testosterone (471).

Biotin in both sexes.—Male rats are more sensitive to biotin deficiency than females. Okey *et al.* (472) find that stilbestrol exerts some protection to the castrate male against the deficiency disease, alopecia. Estrogen elevates the total biotin activity in the blood of sexually immature chicks [Hertz *et al.* (473)]. Ratschow (474) studied the action of sex hormones on circulatory drugs.

Vitamin deficiency effects.—The effects of vitamins and deficiencies on the reproductive organs have been studied extensively. Mayer & Truant

(475) suggest that vitamin A deficiency in rats interferes with the synthesis or release of androgen, and Behr & Gaebler (476) made observations on nicotinic acid, riboflavin, allantoin, ascorbic acid, and vitamin A during anabolism induced by hormones. Hökfelt (477) studied the ascorbic acid concentration in the blood of rabbits. Lillie *et al.* (478) studied the role of vitamin B₁₂ in reproduction in poultry. The influence of two different fats on reproduction was investigated by Dam *et al.* (479). Haque *et al.* (480) report that symptoms of vitamin deficiency in chicks were not relieved by sex hormones. In older vitamin E deficient rats, P'an *et al.* (481) observed an increase in the amount of gonadotropin and Blandau *et al.* (482) studied ovulation, fertilization, and transport of ova. Size and oxygen consumption in fertilized hen eggs have been reported by Smith & Kleiber (483), and Csonka & Olsen (484) report a growth factor transmitted by the hen through the egg to her progeny. Finkler (485) presents some effects of vitamin E on the menopause.

Emotional factors.—There is evidence that emotional factors play an important role in the problems of early infancy (486) and in gynecology (487), and that there is some common factor in both dysmenorrhea and the nausea and vomiting of pregnancy (488).

Old age changes.—In the uterus of the postmenopausal woman, fibrosis and hyalinization occur in the endometrial stroma (489). In the aging hamster, the connective tissue fibers increase in thickness and density, and the circular layer of muscle degenerates (490). In the male, there is a syndrome characteristic of the climacteric (491).

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BLOOD VOLUME¹

BY MAGNUS I. GREGERSEN

College of Physicians and Surgeons, Columbia University, New York, N. Y.

The subject of blood volume is generally regarded to be both confusing and unsettled. A contributing factor to this confusion has been the steady procession of controversies over methods and interpretations of results. Yet it is significant that this attitude has failed to discourage fruitful applications of blood volume determinations in a large variety of biological and medical problems. Whether or not the estimates are conceded to represent "the true blood volume," the fact remains that they have greatly extended our knowledge of blood volume in health and disease and have provided the basis for notable progress in the study, prevention, and/or treatment of disorders involving changes in volume and composition of the blood. These convincing demonstrations of the importance and value of the measurement have intensified the interest in testing, improving, and simplifying older or existing methods and in devising new ones. The large variety of methods now being tried and the fact that the investigator who uses even one of them is likely to become entangled in the technical and theoretical problems common to all methods of measuring blood volume have given rise to a voluminous literature, some of which is impossible to evaluate. Nevertheless, as may be seen from Reeve's excellent and objective assessment of the leading methods (1), there is no longer much foundation for the view that none of the methods is valid simply because they do not all give the same values for total blood volume. On the contrary, the difference in what is being measured by various techniques can be a useful tool of investigation (2).

Methods of estimating blood volume that involve large alterations in volume [the so-called dilution methods described by Erlanger (3)] are not generally applicable, but this principle has recently been put to good use by Phillips, Yeomans, Dole, Farr & Van Slyke (4) and by Strumia, Wall & Strumia (5) in studies on man and by Lawson and his co-workers in studies on dogs (6 to 9).

All other methods for estimating blood volume in the intact animal or man are fundamentally identical in principle. All depend on estimating the dilution in the blood stream of a small but known amount of some innocuous test substance. The test substances fall into two categories: (a) special erythrocytes that can be identified (marked cells) or substances incorporated in the erythrocytes (radio phosphorus, radio iron, carbon monoxide) which, therefore, measure the volume of red cells, and (b) substances that combine with the plasma proteins (dye) or because of size (antigens) are believed to have a similar volume distribution, and therefore, measure plasma volume. It should be noted that none of the tests so far devised directly measure the

¹ This review considers specific aspects of the problem of blood volume and, therefore, refers to old as well as recent papers.

total blood volume. Furthermore, none of them measures directly the volume of white cells in the circulation, although a recently described method of tagging the white cells with radioactive phosphorus (10) may throw some light on this interesting problem. This relatively small and variable part of the blood volume is usually ignored. For example, in calculating the total blood volume from the plasma volume and the hematocrit, few investigators state whether or not the "buffy coat" is included in the estimate of the relative cell volume.

There are three ways of arriving at a value for total blood volume: (a) determine the plasma volume and divide this value by the percentage of plasma estimated from the hematocrit $[(\text{plasma volume in milliliters} \times 100) / (100 - \text{hematocrit per cent})]$; (b) determine the red cell volume and divide this value by the hematocrit $[(\text{total red cell volume in milliliters} \times 100) / (\text{hematocrit per cent})]$; and (c) determine both the plasma volume and red cell volume simultaneously. Most published results have been based on the first procedure using the dye T1824 for measuring plasma volume. In general, it gives higher values than the second, based on measurement of red cell volume. These discrepancies in estimates of total blood volume may be said to constitute the central problem which, in recent years especially, has led to numerous attempts to make direct comparisons of cell and plasma methods by simultaneous measurements.

Combined measurements with carbon monoxide and dye.—Combined tests with carbon monoxide and dye (brilliant vital red) were carried out by Smith, Arnold & Whipple in 1921 on dogs (11) and by Smith, Belt, Arnold & Carrier in 1924 on man (12). They found blood volumes with carbon monoxide to be 20 to 30 per cent lower than with the dye method and concluded that this was caused by differences in cell-plasma ratios in large and small vessels. In 1940, Bazett, Sunderman, Maxfield & Scott (13) in tests on normal men reported that the average blood volume with carbon monoxide was only 7 per cent lower than with dye (Congo red). Subsequently, Asmussen (14) claimed that the carbon monoxide blood volume was consistently higher than the dye (T1824) blood volume, whereas Hopper, Tabor & Winkler (15), Hopper, Winkler & Elkinton (16), and Hevesy, Köster, Sørensen, Warburg & Zerahn (17), also using the dye T1824, found that the average values were not significantly different, although individual tests reveal large differences. With improved carbon monoxide and dye methods, Root, Roughton & Gregersen (18) attempted a series of critical comparisons on dog and man under various conditions of peripheral vasoconstriction and dilatation, but they could not find evidence that the alterations in the amount of blood in small vessels and capillaries influenced the ratio of carbon monoxide blood volume to dye blood volume as would be expected from Whipple's earlier reasoning (11). In 11 normal subjects at rest, the average ratio of carbon monoxide to dye blood volumes was 0.99; the range was 0.92 to 1.04. Another series of tests which appear to be carefully controlled have recently been reported by Courtice & Gunton (19, 20). In these, the average ratio of

carbon monoxide to dye blood volume was 1.03 in man and 1.02 in the rabbit.

Technical improvements have thus closed the gap between results with carbon monoxide and dye, but the outcome must be regarded as fortuitous since evidence from various sources leads one to believe that carbon monoxide to some extent overestimates the red cell volume (2, 18, 19, 21).

Combined measurements with radioactive iron (tagged cells) and dye.—Hahn, Ross, Bale, Balfour & Whipple (22), in the original studies (dogs) with cells tagged with radioactive iron, found blood volumes far below those estimated with the dye method (brilliant vital red). Comparisons with radio iron and T1824 have subsequently been made on dogs and man by Gibson, Peacock, Seligman & Sack (23) and on man by Meneely, Wells & Hahn (24). Because of the manner in which the data are reported, it is simpler here to compare the ratio of red cell volume by radio iron to red cell volume by dye method. In 40 dogs, Gibson and his co-workers found that this ratio ranged from 0.62 to 0.98, the average being 0.82. In 40 young men, the range was 0.70 to 0.95, the average, 0.85. Reeve & Veall (25) have pointed out that correction of the hematocrit values (plasma trapping) used in the calculations would raise the average in these tests on man to 0.87. According to the results reported by Meneely, Wells & Hahn on 28 patients, the average ratio is about 0.81, but, it should be noted that in the conclusion of their report, Hahn and his colleagues emphasize the great variability in the discrepancy between the two methods of measuring blood volume. This variability, which is apparent in the values just quoted from the report of Gibson and his co-workers (23) and can be observed also in tests by Nickerson *et al.* (32), has recently been investigated by Nickerson, Gregersen, Root & Sharpe (26), who find that blood incompatibility lowers the value obtained with radio iron but does not apparently affect the dye (T1824) measurement. The same effect can be demonstrated with the carbon monoxide method by infusion of incompatible carbon monoxide saturated blood (26). Under these conditions, a large discrepancy appears between the carbon monoxide blood volume and the dye blood volume even though, as in the experiments with radio iron, the dog may fail to show any outward signs of untoward reactions. Further work on this complicating factor appears to be necessary before the results with cell-tagging methods can be finally evaluated.

Combined measurements with radioactive phosphorus and T1824.—All investigations referred to here have been performed on man. Mayerson, Lyons, Parson, Nieset & Trautman (27, 28) have reported close agreement between P^{32} and dye blood volumes, but these workers used a large hematocrit correction factor (29) which tends to obliterate the discrepancy. Their results do not, therefore, agree with the earlier reports of Hevesy and his co-workers (17) nor with the recent results reported by Nachman, James, Moore & Evans (30) on 38 ambulatory patients in which the ratio of P^{32} red cell volume to dye red cell volume ranges from 0.58 to 0.98, the average being 0.80. The large range of discrepancies may signify occasional clumping reactions which have been observed *in vitro* when P^{32} saturated cells are

mixed with the fresh blood (26). More consistent results have been reported by Reeve & Veall (25), whose experiments are notable for the care with which both the dye and P^{32} determinations were made. In 13 normal subjects, the ratio of P^{32} red cell volume to dye red cell volume ranged from 0.83 to 0.92, the average being 0.87. It is significant that this average ratio agrees closely with that reported by Barnes, Loutit & Reeve (31), using the Ashby marked cell method and T1824. In a group of 20 tests on normal subjects and hospital patients, the average ratio was 0.88; on the normal subjects alone, it was 0.89.

The results summarized above thus lead one to the conclusion that the difference between total blood volume as measured by the T1824 hematocrit method and as estimated from the cell volume and the hematocrit value (corrected for plasma trapping) is of the order of 12 per cent (25). This difference could arise from (a) underestimation of the cell volume with tagging methods, (b) overestimation of the plasma volume with T1824, (c) error in the determination of the true relative cell volume (hematocrit), and (d) actual differences in the distribution of cells and plasma in the circulation. Underestimation of red cell volume with cell-tagging techniques has, so far as current evidence justifies, been taken into consideration by the writer, although, as noted above, some additional tests may be needed to reach a final decision. The remaining three possibilities will be considered below.

PLASMA VOLUME

Inasmuch as the literature on dye methods was summarized in some detail only two years ago by Reeve (1), a great deal of the material that would ordinarily come under consideration here will be omitted. Attention will be given only to special aspects of the problem and to recent evidence related to the question of the validity of the measurements, particularly the measurements with T1824, since this is the most widely used technique.

Determination of plasma concentration of T1824.—For the measurement of plasma volume on normal individuals, it is unnecessary to standardize the dye in the plasma of each subject. Within the limits of experimental error the "magic number" [optical density of a standard dilution, usually 1:500, of dye in plasma (36)] seems to be the same in all normal human plasmas. It must be emphasized, however, that little or nothing is known about the effect of disease on the spectral characteristics of T1824, and this might be important both practically and theoretically. One of the puzzling problems is the species difference in the "magic number" (33). These are questions that deserve more attention than they have received.

In single beam instruments (all photoelectric photometers or colorimeters), a high background density may introduce undetected errors if the densities below which the instruments function on a linear basis are exceeded [see (34, p. 160)]. This point must be emphasized because it is apparent that many workers have been unaware of the danger, especially with repeated dye injections. Two-beam instruments, such as the König-Martens spectro-

photometer or the much simpler Nickerson Decade Photometer (35, 36), have the great advantage that the difference in density between the control and unknown is read directly and is independent of the level of background density.

In addition, there are several well recognized and particularly troublesome factors related to background color of plasma that can disturb the accuracy of measurement of the plasma dye concentration. The outstanding ones are (a) turbidity caused by lipemia, which gives a large and unsteady background density even at 620 to 625 $m\mu$ [see for example (36, 37)], (b) hemolysis in either the dye-free or dye-tinged samples, (c) stasis during the withdrawal of the blood samples, and (d) fluid shifts or rapid changes in plasma volume. The last two also influence the dye concentration, but under certain conditions useful corrections can be made from the concomitant changes in the plasma protein concentration (34, 36), and these corrections must be made in order to estimate correctly the disappearance rate of the dye. The errors arising from the alterations in the background density are much more difficult to get at, and as emphasized by Ebert & Stead (38), these changes constitute a valid criticism of the use of changes in the dye curve for estimating rapid changes in plasma volume, especially when the ratio of dye density to background density is low. However, in one set of observations on muscular exercise (39) referred to by Ebert & Stead, the plasma dye concentration was fairly high and the percentage of change produced by the short bout of exercise was not far different from the changes in both plasma protein and hematocrit values. In the exercise studies of Kaltreider & Meneely (40) less dye seems to have been used and therefore changes in background density may have played a somewhat larger role. In principle, however, Ebert & Stead (38) are perfectly correct. Spectrophotometric corrections for hemolysis have been proposed, but they are laborious and, in the writer's opinion, unsatisfactory.

Because of these various difficulties, the advantages of a procedure for the quantitative extraction of dye from the plasma have long been recognized. Hamilton (41, 42) has for several years used alcoholic extraction of brilliant vital red, and Dow & Pickering (43) have recently made an interesting study of this procedure. Various methods for extracting T1824 have been proposed by Harington, Pochin & Squire (44), Croke & Morris (45), Phillips (46), Morris (47), Chinard & Eder (37), and by Leeson & Reeve (48). None of these procedures are ideal either because they are too complicated for routine use, because they utilize strong reagents (acids or alkalis) which may affect the stability of the dye, or because they fail to extract the dye quantitatively and without contamination under all circumstances. Recently, Allen (49) has worked out an extraction method which seems to be both adequate and simple. The dye-tinged plasma is mixed with soap, sorbed on a column of paper pulp, washed with saline, and eluted with a mixture of acetone and water. The recovery of T1824 from aqueous solutions, clear plasma, grossly hemolyzed plasma, lipemic plasma, bile, or urine

is claimed to be consistently 97 per cent ± 1 per cent. Furthermore, the spectral absorption curve of the final solution is identical with that given by adding pure T1824 to the eluent, demonstrating the completeness of the separation from the hemoglobin, fat, and other constituents in the original samples.

If the batch of T1824 used in measuring plasma volume contained colored impurities that escape rapidly from the circulation, the volume will, of course, be overestimated. With this in mind, Leeson & Reeve (48) have examined various preparations of T1824 and in the purest of these [from Warner Institute (36)] found as much as 2.5 per cent of red or purple impurity, but it should be noted that Leeson & Reeve used an aluminum oxide sorption column and alkaline eluents which may affect the stability of the dye. Allen (49, 50) finds less than 0.5 per cent red impurity in the same preparation, which strengthens the conclusion of Leeson & Reeve (48) that at least this batch of T1824 (and perhaps others) is sufficiently pure to exclude significant errors arising from the presence of red impurities.

In conclusion, it should be emphasized that with proper technique and appropriate precautions, the determination of the plasma concentration of T1824 can be accurate within ± 1 per cent. Even in *in vitro* experiments with whole blood, where a considerable part of the error is related to the measuring and handling of the blood and in the determination of the hematocrit, the difference between the measured and determined volume is easily within ± 2 per cent [see for example (18)]. Overestimation of plasma volume arising from technical procedures seems, therefore, to be excluded as a possible cause of the discrepancy in plasma and cell methods of measuring blood volume.

Is the volume distribution of T1824 equivalent to the plasma volume?—The time required for uniform mixing and the amount of dye lost during this so-called mixing period has been the subject of incessant controversy since Keith, Rowntree & Geraghty (51) introduced the dye method. Erlanger (3) devoted considerable space to these questions in his review, as has almost every subsequent author who has considered the question at all. Extrapolation of the disappearance curve to the time of injection, suggested by Erlanger (3), came into use about 15 years ago and since then has been standard practice among careful workers. However, evidence has been accumulated (34, 36) showing that in man the error in calculating the volume from a single blood sample taken at 10 min. is for practical purposes not likely to be significant. Extrapolation on a semilog plot (52) is usually simpler than on a linear plot and is theoretically preferable (52, 53). Other methods of plotting the dye curve have been proposed (7, 54).

Hamilton (42), Gilder, Müller & Phillips (55), Cruickshank & Whitfield (56), and others who believe that mixing occurs in less than 5 min. have recommended calculating the volume from very early samples. According to this view, the early decline in the dye curve is not caused solely by mixing but by an initial rapid loss of dye. Some of the observations most frequently cited in support of this concept are that there exist evidences of tissue stain-

ing, phagocytosis, and the appearance of dye in the lymph (57, 58) and bile (59) soon after injection, that dye concentrations in blood samples drawn simultaneously from various parts of the vascular bed are identical within a couple of minutes (55, 56), a period of time which, in any event, would be ample for the dye-tinged blood to traverse the slowest circuits, and that since tagged cells are mixed within 2 to 4 min., as shown for example by Hahn *et al.* (22), then dye should not require a longer period. Some of the experiments Lawson and his associates (6 to 9) have carried out, which unfortunately are open to question because of the experimental conditions (anesthesia and major surgery), also indicate that a significant fraction of dye is rapidly lost from the circulation. One report in particular (56) seems to have brought the controversy to a head despite the poorly controlled experiments purporting to demonstrate the phenomenon now variously referred to as the "cat effect" or "gobbling." However, the attention which the work of Cruickshank & Whitfield (56) has received may be accidental since the implication that T1824 overestimates plasma volume has, in the meantime, become a question of major interest in connection with the attempts to trace the reasons for the discrepancy in blood volume determined by plasma-dye and cell-tagging methods.

Some of the evidence against initial rapid loss of dye is as follows: (a) Nylin's mixing curves for P^{32} tagged cells (61) and the tests made by Barnes, Loutit & Reeve (31) with Ashby's marked cell method and T1824 do not indicate that the mixing time for cells is very different than for dye; (b) the "cat effect" is disproved by the fact, long known, that under properly controlled conditions, repeated injections of dye give the same plasma volume [(62, 63) and many others]; (c) furthermore, the value obtained for plasma volume is the same with small as with large injections of dye (64) even up to 20 times the usual amount employed in determinations (65). The binding of T1824 by plasma albumin demonstrated by Rawson (66) provided a reasonable explanation for the slow disappearance of the dye (52) and made it seem likely that the volume distribution of T1824 is the same as albumin. The recent work of Allen & Orahovats (50, 67, 68) lends support to this view by showing that T1824 is an effective albumin-tagging agent, the ratio of bound to free dye in the plasma being 1,000:1, and that even liver slices (68) have difficulty competing with albumin for the dye. LeVeen & Fishman (69) have also studied the binding of T1824 with proteins, emphasizing certain limitations of the dye as a tagging agent. According to Miller's evidence (59, 60), uptake of T1824 by the liver is apparently not rapid enough to influence the disappearance curve significantly. However, it should be noted that T1824 disappears rapidly from the blood of patients with amyloidosis (70). Another, and perhaps the most decisive line of evidence, is derived from direct comparisons of plasma volume measured with T1824 and antigens (71) or radio-iodo-albumin (72). The volume distribution of the three antigens, bovine albumin, bovine globulin, and the polysaccharide SIII, is, within experimental error, the same as T1824 (71). Results with the radio-iodine

method differ somewhat; those of Gibson *et al.* (72) and of Crispell, Porter & Nieset (73) agree with the dye-volumes, whereas Krieger, Storaasli *et al.* (74, 75) report the dye values to be higher. However, the latter workers used a dye procedure (single sample) which is scarcely accurate enough for such critical tests on dogs.

Thus, if the plasma volume is defined as equivalent to the volume distribution of plasma proteins and other colloids of similar size, then it may be concluded with considerable certainty that T1824 does not overestimate the plasma volume (71).

MISCELLANEOUS METHODS OF MEASURING BLOOD VOLUME

Other methods that have come to the writer's attention include the following: (a) the "Geigyblau" 536 technique (84) recently used by Nizet & Barac (85) in a comparative study with T1824 and with the phenylhydrazine marked-cell method of Nizet (86), (b) tagging of cells with methemoglobin, (87) a method open to question because methemoglobin in the circulation reverts to oxyhemoglobin, (c) measurement of plasma volume with the plasma substitute "subtosan" (polyvinylpyrrolidone) by Poullain & Piette (88), (d) with more exact methods of determination, the possible use of the polysaccharide, Dextran, for measuring plasma volume, (e) tagging of red blood cells and plasma proteins with radioactive chromium, which has been reported by Gray & Sterling (89).

HEMATOCRIT

Since the hematocrit value enters into the calculations of total blood volume, the correction applied to the hematocrit value for plasma trapping is of importance in accounting for the discrepancy between cell and plasma methods. The variability in estimates of the true relative cell volume with different methods has been examined by McLain & Ruhe (76), but these authors also report large variations with individual methods (e.g., 0-17.7 per cent trapping with T1824 method) which are not explained and which are much greater than these reported by others (80, 81). Jackson & Nutt's recent studies (77) again emphasize, as have earlier studies on the hematocrit method (Millar, Ponder, and others), the relation between the degree of packing and the force and duration of centrifugation. Using T1824 for estimating plasma trapping, they find values ranging from 17 per cent to 0.8 per cent, depending on the centrifugal force applied (541 to $6,000\times g$). Above $1,500\times g$ (i.e., 3,000 r.p.m. with a radius of 15 cm.), the curve relating percentage of trapping to relative centrifugal force flattens, showing the importance of maintaining the relative centrifugal force at or above this level in order to obtain consistent values.

The magnitude of the correction factor that should be applied under standard centrifugation conditions (usually $1,500\times g$ for 30 min.) has been estimated by other investigators. Three reports (29, 78, 79) claim that

the percentage of plasma trapping is of the order of 8 to 9 per cent. Of these, the one by Chapin & Ross (29) has had considerable influence on current opinion in spite of a large body of evidence indicating that their value for some unknown reason is too high (31, 71). The correct value lies between 3 and 5 per cent (1, 31, 71, 77, 80 to 83). Reeve (1) and his colleagues use a correction factor of 0.95, and in the writer's laboratory where the percentage of trapping has also been repeatedly checked (33, 36, 71, 80), the factor of 0.96 has been adopted. Thus, plasma trapping, if ignored, accounts for not more than 5 per cent of the discrepancy in cell and plasma methods of estimating total blood volume.

UNEQUAL DISTRIBUTION OF CELLS AND PLASMA

Early evidence is discussed by Smith, Arnold & Whipple (11), and a recent summary is given by Reeve (1). It is generally presumed from the various lines of evidence, which is admittedly qualitative (1), that the marginal layer of plasma in the small vessels and capillaries must be mainly responsible for whatever real discrepancy exists between cell and plasma methods of estimating total blood volume. The question may be raised as to whether or not the volume of blood in this portion of the vascular bed is large enough to account for the discrepancy (18). Indeed, one is inclined to suspect that there may be more to this problem than at present meets the eye. For example, cells appear to be sequestered after extensive blood loss (90, 91) and after extensive surgical procedures [(92) and others]. On the contrary, following injections of Dextran in normal subjects, there is indication of release of red cells (93, 94), although neither exercise (39, 40, 95, 96), nor epinephrine (97, 98) reveals the existence in man of red cell depots of any significant size. Further investigation may disclose that some hitherto unsuspected mechanism is involved in the unequal distribution of cells and plasma.

BLOOD VOLUME AND ITS VARIATIONS

Space does not permit an extensive coverage of the literature, nor would this be particularly useful in view of the obvious difficulty in evaluating many of the results. References to other data may be found in several of the papers that will be mentioned here or in the bibliography listed by Reeve (1).

Normal values have been reported on a number of the common laboratory animals (1), but beyond this, little has been done in the comparative physiology of blood volume. Results on dogs are most abundant. Recent values obtained with the T1824 method have been reported by Bonnycastle (99) who refers to the work of others. In three separate samplings (30 mongrel dogs in each), one group of investigators (100, 101, 102) found little difference in the mean values, expressed in cubic centimeters per kilogram of body weight (96.7, 99.1 and 97.9), although individual variations are large and may be related to type or breed (103). Among recent reports on other species, several on rats (104 to 109) and one on chickens (110) may be noted.

The establishment of average normal values on man has been the object of many investigations (3, 23, 111 to 120), but individual variations in the data limit the experimental and clinical use of mean values. Attempt has been made to relate the variations to the body type (120). Blood volumes in women are reported to be lower than in men (112, 114, 119). Recent data on infants and children has been published by Morse, Cassels & Schultz (121) and by Russell (122) [see Reeve (1) for earlier reports]. Cohn & Shock (123) conclude from their own and other data (114) that in males there is no significant change in blood volume with age (20 to 90 years). Racial differences in blood volume, if present, are difficult to demonstrate (118) since other factors are involved (120).

A number of references to observations on the effects of environmental temperature, pregnancy, muscular activity, training, posture, epinephrine, excitement, etc. are given by Reeve (1). Since then, a comprehensive monograph on various aspects of starvation, including blood volume changes, has been published by Keys and his associates (124). Gollan (125) has reported observations on undernourished children. As the body weight declines, the total plasma volume is maintained, and therefore, the plasma volume per kilogram of body weight is abnormally high (116, 124, 125). Decline in physical fitness with prolonged bed rest is accompanied by reduction in blood volume (126).

Huey & Holmes (127) have collected data on normal blood volumes at moderate altitude (5,280 ft.), and Holmes *et al.* (128) have observed reduction in plasma volume by inhalation of high carbon dioxide mixtures. Henry *et al.* (129) report that pressure breathing causes slight reduction in plasma volume. There are several recent papers on the increased blood volume in pregnancy [(1, 130 to 133) and others], and Freis & Kenny (134) report low blood volumes in pre-eclampsia and eclampsia. Sympathectomy increases the plasma volume in cats (135) but has no effect on blood volume in dogs (136, 137). Likewise, in man (hypertensive patients) sympathectomy does not appear to alter the blood volume (138, 139).

There are many scattered observations on the effects of drugs and anesthetics which will not be considered, but it may be noted that the effects of anesthetics on blood volume per se are far less important than the lowering of resistance to blood loss. The depressing effect of anesthesia on the compensatory reactions to hemorrhage is strikingly shown by the much lower bleeding volumes in anesthetized than in unanesthetized dogs (140). Observations on the effect of anesthesia on compensatory dilution after hemorrhage are reported by Courtice & Gunton (141).

Research on wound shock and hemorrhage during World War II demonstrated the importance of reduction in blood volume as a causative factor [(142, 143) and many others]. As a consequence, there has been growing interest in the study of blood volume on surgical patients. A partial list of recent papers is sufficient to indicate the great activity in this field (92, 117, 144 to 147). One of the interesting facts reported is the frequent discrepancy

between external blood loss (collected) during major operations and the measured decrease in blood volume, corresponding to the results obtained on dogs (90, 91). Patients undergoing surgery are less resistant to hemorrhage than unanesthetized subjects (92, 148), but the reviewer has not found any study of the influence of anesthetics and drugs on the resistance to blood loss in obstetrical cases. In patients with chronic infection, the blood volume is much reduced, and in some of these and in anemic patients, total blood volumes of less than 2 l. have been observed, demonstrating a remarkable adaptation to reduced blood volume, when brought about gradually. Agress, Rosenburg, Schneiderman & Brotman (149) find that in shock resulting from myocardial infarction, the blood volume undergoes little change. The evidence from dye measurements that blood volume increases in congestive heart failure is questioned by Ross, Baker & Freis (150), who claim that the tagged cell method P^{32} shows no change.

The relation of blood volume to water and electrolyte balance (39) has been the subject of a number of investigations on animals and man. A partial list of contributions includes those of Mellors, Muntwyler, Mautz & Abbott (151), Nadal, Pedersen & Maddock (152), Hopper, Elkinton & Winkler (153), Elkinton, Danowski & Winkler (154), Painter, Holmes & Gregersen (155), and Cizek, Semple, Huang & Gregersen (156).

It is obvious that many questions relating to blood volume have been omitted, among them the all important one of the mechanisms regulating blood volume. The maintenance of blood volume can be considered to depend on three groups of mechanisms: (a) those concerned with control of plasma volume, (b) those concerned with the production and destruction of erythrocytes, and (c) the master mechanisms, responding to disturbances in the total blood volume. Some of the evidence bearing on this problem has been referred to, but a satisfactory treatment of the subject is beyond the scope of this review.

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